Neurology

OFFICIAL JOURNAL OF
THE AMERICAN ACADEMY OF NEUROLOGY

OCTOBER--1955

Volume 5 — Number 10

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1. Palmer, H., and Gallagher, D. J. A.: Brit. M. J. *2*:558 (Sept. 2) 1950. 2. Ziegler, D. K., and Torres, F.: Neurology *5*:197 (March) 1955. 3. Timberlake, W. H., and Schwab, R. S.: New England J. Med. *247*:98 (July 17) 1952.

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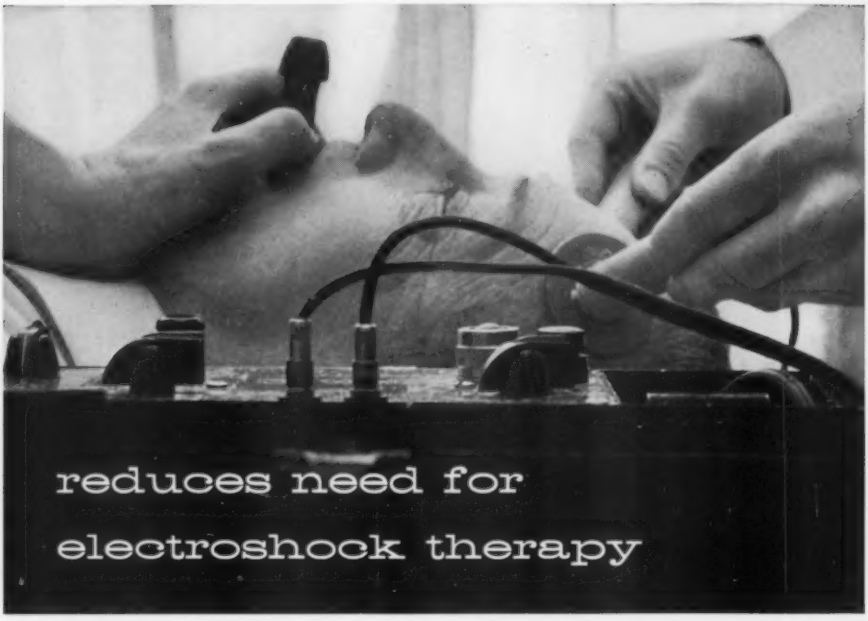

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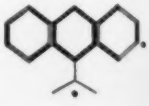

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INFORMATION FOR *Authors*

NEUROLOGY, the official publication of the American Academy of Neurology, has been instituted to provide a medium for prompt publication of articles dealing with neurology and its cognate fields and to stimulate individual investigation in these various fields.

Manuscripts of papers read at meetings of the Academy must be filed with the secretary at the time of the meeting, and will be published if acceptable to the editorial board. They are the property of the Academy, and authors who wish to publish them elsewhere must first request release.

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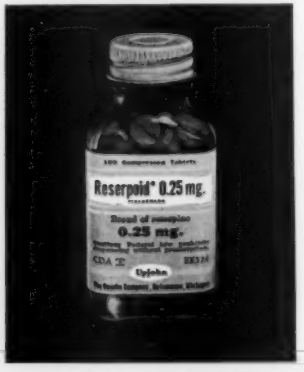

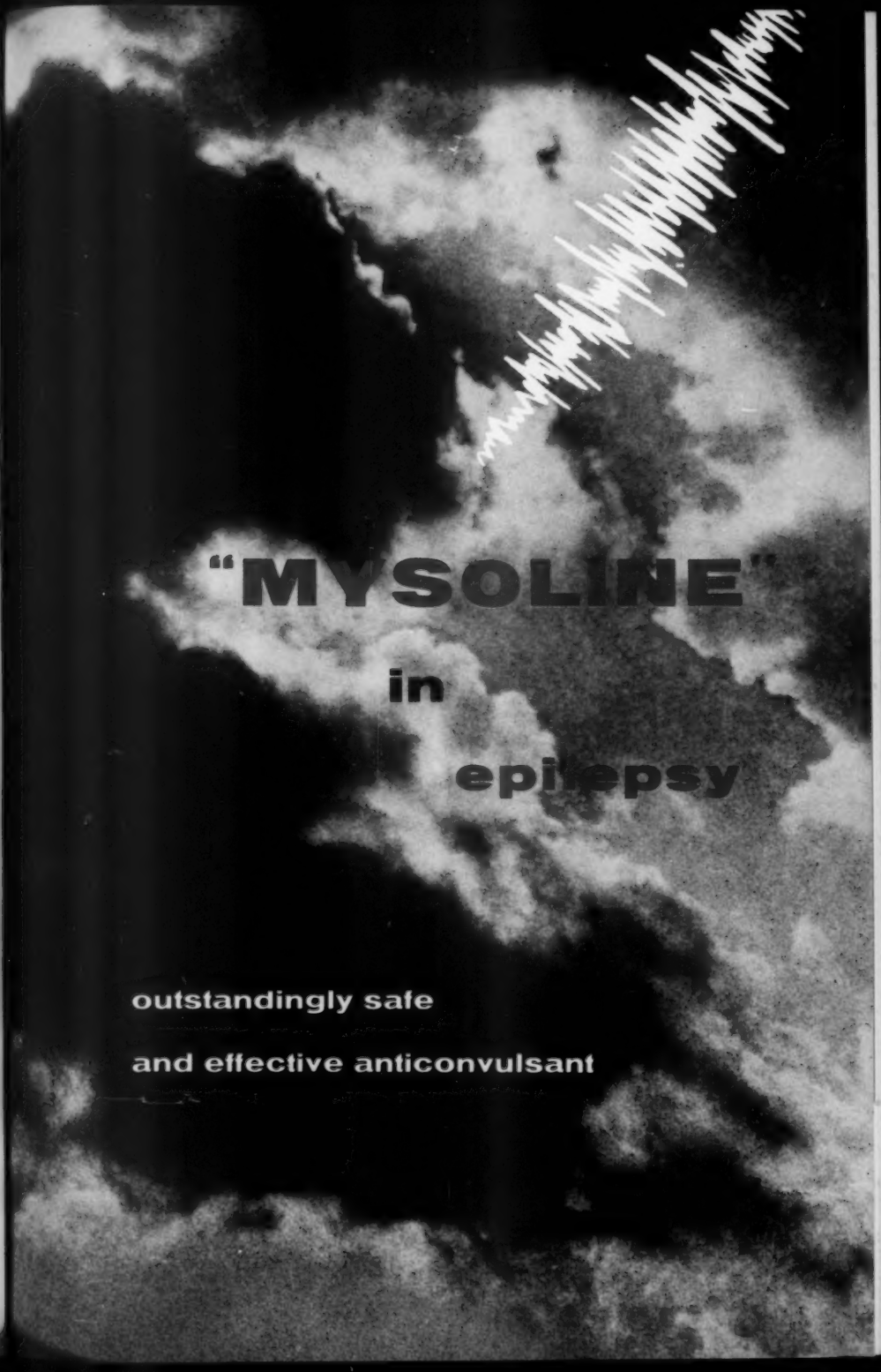
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1. Smith, B., and Forster, F. M.: Neurology *4*:137 (Feb.) 1954. • 2. Editorial: Brit. M. J. *1*:1028 (May 1) 1954. • 3. Lambros, V. S.: Read before the Annual Meeting of the American League Against Epilepsy, Washington, D. C., May 1, 1954. • 4. Smith, B. H., and McNaughton, F. L.: Canad. M.A.J. *68*:464 (May) 1953. • 5. Doyle, P. J., and Livingston, S.: J. Pediat. *43*:413 (Oct.) 1953. • 6. Pence, L. M.: Texas State J. Med. *50*:290 (May) 1954.

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Electroencephalogram showing typical wave pattern of a patient with grand mal seizures.

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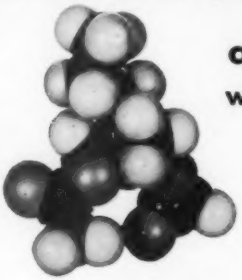
Two articles in the April 30th issue of The Journal of the AMA[1,2] report on . . .



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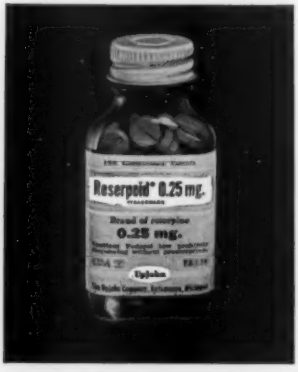

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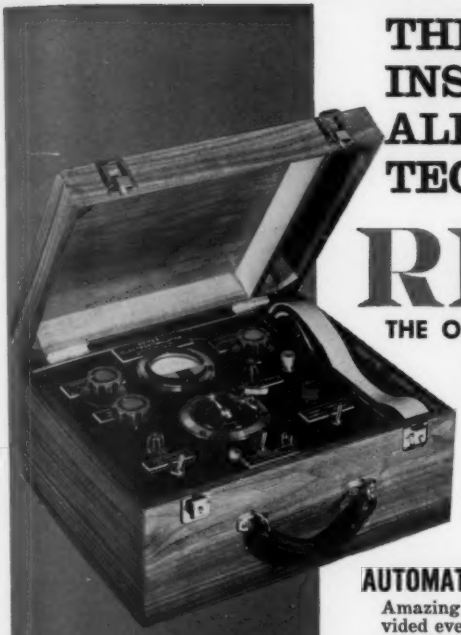

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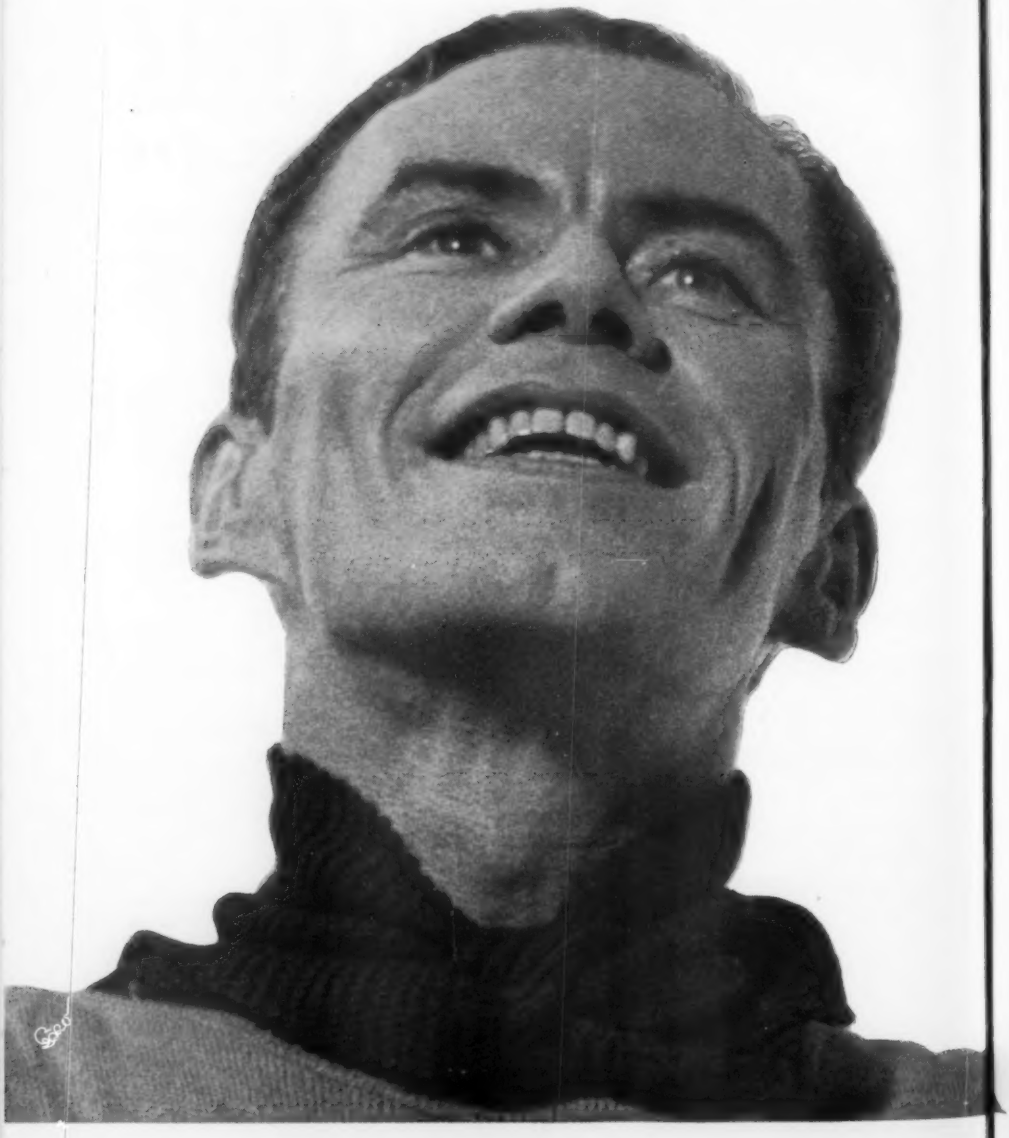

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Volume 5 Neurology Number 10

Neurologic Complications of Pregnancy

J. Preston Robb, M.D.

THE NEUROLOGIST is frequently called to see patients who, during the course or termination of pregnancy, have developed some affliction of the nervous system requiring prompt action to save the life of the mother or child. Some of the questions asked are, "Should the pregnancy be terminated? Should an immediate cesarean section be done? Should labor be induced? What medication can be used to control seizures?" and so on. It is with this thought in mind that some of the neurologic complications of pregnancy are considered. Von Hösslin[1] in 1904, Alpers and Palmer[2] in 1929, King[3] in 1950, and others in greater or lesser detail have reviewed these problems extremely well. It is the purpose of this paper to review some of the fluid, electrolyte, and endocrine changes associated with pregnancy and attempt to correlate these with some of the neurologic complications of pregnancy. At the same time, some of the current opinions regarding therapy will be reviewed. Pregnancy may be the direct cause of some conditions; it may aggravate already existing conditions, while in some instances an existing condition may improve. Although the exact relationship between the neurologic condition on the one hand and the endocrine, electrolyte, and blood changes on the other is often not known, it is profitable to review them and, as our knowledge advances, to continue to review them.

The following is an outline of the problems to be considered:

1. *Physiologic background*
   - Endocrine changes
   - Electrolyte changes
   - Fluid and blood changes
2. *Inflammatory conditions*
   - Virus disease
   - Bacterial diseases
   - Chorea gravidarum
3. *Vascular and related conditions*
   - Toxemia
   - Migraine
   - Subarachnoid hemorrhage
   - Puerperal hemiplegia

From the department of neurology and neurosurgery, McGill University, and the Montreal Neurological Institute, Montreal.

Read at the seventh annual meeting of the American Academy of Neurology, Houston, Texas, April 29, 1955.

4. *Traumatic and toxic conditions*
   Acute lumbosacral plexus and other peripheral nerve lesions
   Chronic pressure or postural neuropathy
   Protruded intervertebral disks
   Spinal anesthesia
5. *Tumors*
   Primary
   Secondary
6. *Other conditions*
   Epilepsy
   Multiple sclerosis
   Myasthenia gravis
   Nutritional neuropathy or neuritis

1. PHYSIOLOGIC BACKGROUND

The Endocrines

In addition to the changes in the organs of reproduction, the body as a whole participates in biochemical alterations of water, electrolyte, carbohydrate, fat, and protein metabolism. Many of these changes are the result of increased elaboration of steroidal hormones.

Very early in pregnancy there is a rapid rise of chorionic gonadotrophin production, as shown in figure 1 from Venning.[4,5] It reaches a peak between the 50th and 70th day, then falls off until the 110th and 120th, where it remains fairly constant at a low level until the end of pregnancy.

Early in pregnancy progesterone and estrogen are produced by the corpus luteum, but this function is gradually taken over by the placenta. As progesterone is metabolized rapidly in the body, it is measured in humans by its chief metabolite, pregnanediol. The urinary excretion of pregnanediol glucuronide is a reflection of the amount of progesterone elaborated (figure 1). The production of progesterone and estrogens increases gradually over the first three months and then more rapidly until at the end of pregnancy they are both being produced in relatively large amounts, the rate of estrogen elaboration increasing more rapidly than that of progesterone.

In 1926 Hisaw,[6] in seeking a physiologic basis for relaxation of pelvic ligaments, found it was under hormonal control. A substance, which he called relaxin, was in the blood of pregnant guinea pigs in increasing amounts as the pregnancy advanced. Serum from a pregnant guinea pig injected into a virgin guinea pig produced relaxation of the pelvic ligaments. It was also shown that the animal must be under the influence of the follicular hormone before the relaxin could produce its characteristic effect. He was able to show that it is a special fraction of the corpus luteum hormone. Pommerenke[7] showed that serum taken from pregnant women in the early months of pregnancy contained a substance capable of relaxing the pelvic ligament of castrated female guinea pigs who had been artificially brought into estrum. Serum taken later in pregnancy did not have the same relaxing effect. The whole explanation was not clear.

It is clear there is increasing relaxation of pelvic ligaments in women as they approach term, and this is probably dependent on a hormonal effect.[8] We must stop to consider what effect this relaxing hormone has on other parts of the body. What effect does it have on the strength of vessel walls or the connective tissue holding together an aneurysm? What effect does it have on seizures, multiple sclerosis, or the production of brachial plexus compression due to relaxation of the shoulder girdle?

The adrenal gland increases in size during pregnancy, and with this there is an increased production of adrenocortical hormones. Venning and coworkers[9] showed there is an increased

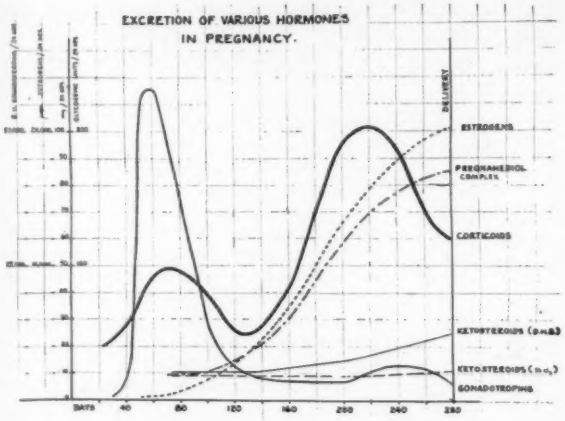

FIG. 1. Excretion of various hormones in pregnancy (from Venning).

excretion of glucocorticoids representing such hormones as hydrocortisone and cortisone in the first trimester, which usually returns to normal levels by the 100th to 120th day. This is followed by a subsequent increase in the output of glucocorticoids which reaches a maximum excretion in the last trimester of pregnancy. Little change was observed in the excretion of 17-ketosteroids in pregnancy.

The thyroid becomes more vascular and usually hypertrophies. There is an increase in the basal metabolic rate and in the serum protein-bound iodine. The significance of the findings is not clear. Active involution of the thymus and other lymphoid organs occurs in pregnancy.

Electrolytes and Water

A study of the endocrines leads one naturally to the increase in water retention seen in late pregnancy, and the progressive increase in plasma and total blood volume which becomes maximum in the ninth month. Taylor, Warner, and Welsh[10] demonstrated that estrogens as well as adrenocortical hormones cause water and sodium retention. The period in which there is a maximum water retention is associated with an increase of estrogens and adrenocorticoids. These hormones should be added to the list of contributing factors such as high sodium intake and lowered plasma protein which may predispose to edema in pregnancy. In the same way, the loss of sodium and water in the puerperium is due to a disappearance of these placental estrogens.

One should also mention the increase in protein uptake. Chesley[11] has shown that there is an average gain in weight of 24 pounds at term. Four pounds of this is due to protein taken up by the body generally and not included in the products of conception or the reproductive organs.

The Blood

Reference has already been made to the blood dilution that takes place with the water retention. As well, there is an increase in blood fibrinogen from 0.3 gm. per cent to 0.4 gm. per cent at or about term. As the other factors are diluted, this is a greater increase than

appears at first. As a result of the dilution, serum proteins are decreased. At term the blood volume increases about 30 per cent, the plasma volume about 40 per cent, and the red cell volume about 20 per cent. As well, in the last trimester there is an increase in the clotting tendency.[12] This undoubtedly is important in some of the vascular changes that are seen so frequently, especially in the puerperium.

2. INFLAMMATORY CONDITIONS

For the most part, pregnancy has little proved effect on inflammatory conditions of the nervous system. German measles early in pregnancy is known to be disastrous to the fetus, but does not have a particular effect on the mother. As far as one can determine, pregnancy does not predispose to the virus encephalitides, but the work of Alpers and Palmer[2] would suggest that the mortality rate is higher in pregnant women than in others. The late manifestations of syphilis,[13] once present, have not been conclusively shown to be altered by pregnancy.

In 1941 Aycock[14] suggested that pregnancy predisposes to paralytic poliomyelitis, but the evidence is not clear-cut. Advanced pregnancy certainly predisposes to respiratory difficulty in poliomyelitis, but this is more mechanical than neurologic. It has been shown that women with severe and varied forms of paralytic poliomyelitis can be carried to term. In the summer of 1953 a patient was seen at the Montreal General Hospital illustrating a practical aspect in treatment.

Case 1.—A 33 year old former nurse of the hospital was admitted with a very stiff neck, headache, and fever. She was eight months pregnant and somewhat overweight. There was no demonstrable weakness, and she was very sick. Lumbar puncture revealed 200 lymphocytes. She either had tuberculous meningitis or poliomyelitis, and we could not afford to wait to find out. Intrathecal and intramuscular streptomycin was started at once, and a few hours later cesarean section was performed, delivering her of a healthy boy. For five days the fever persisted, then fell to normal where it remained. She slowly improved, and it became apparent that she had some gluteal weakness. Subsequently, when she could be properly evaluated, it became apparent that she had weakness of her abdominal muscles. There was no question that she had had poliomyelitis. Whether the advanced state of the pregnancy contributed to the weakness of the trunk muscles remains a question. The point of interest is the difficulty one has in making a diagnosis in a patient with lymphocytic meningitis, stiff neck, and no weakness.

Chorea Gravidarum

Chorea gravidarum is an exception. Pregnancy predisposes to acute chorea and favors a relapse in previously choreic individuals.[15] It is most common in the first trimester. Younger primiparas are more common, but it may appear at second or even in several pregnancies in succession. In 1932 Willson and Preece[16] reviewed 951 cases from their own series and the literature. They found that in one-fourth of the patients there was a previous history of both chorea and rheumatic fever. Approximately two-thirds had one or the other, or both. They concluded that the disease was identical with Sydenham's chorea. Treatment of these patients has been a debated problem. It seems clear that in mild cases there is no reason for therapeutic abortion. In severe cases statistical evidence fails to show that better results are obtained with intervention than without.[17] The treatment of "rest, seclusion, careful feeding, and gentle discipline," recommended by Wall and Andrews[18] in 1903 still seems to be the

method of choice. Willson and Preece suggest that if, in spite of a trial of treatment, the patient continues to deteriorate, with uncontrollable movements, intractable insomnia, exhaustion, and psychotic disturbances, then interruption of the pregnancy should be considered seriously. Whether this will ever be necessary, with the use of chlorpromazine, is difficult to say.

3. VASCULAR AND RELATED CONDITIONS

Toxemia of Pregnancy

It is my understanding that eclampsia is less common today than it used to be. However, the seizures and vascular changes of the brain that accompany eclampsia continue to be among the major neurologic problems of pregnancy. The main physiologic change is the retention of fluid and sodium chloride, with resultant generalized and cerebral edema. Cerebrovascular changes[19] may be arteriospasm, cerebral edema, thrombosis of cerebral vessels, intracerebral hemorrhage, or subarachnoid hemorrhage. All of these may occur with or without convulsions or paralysis. Treatment is directed first at the toxemia and secondly at the specific cerebral condition. Rational therapy includes forced fluids, salt-free diet, and anticonvulsants. Arnell[20] had a remarkable series of 142 cases without a maternal death. His therapy consisted mainly of a high-protein, salt-free, 2,000 calorie diet, with four or more liters of fluid a day, to be taken orally if possible. His review covers the whole problem and provides a good guide for anyone confronted with an eclamptic patient.

As a neurologist, one will be asked whether the cerebral condition demands cesarean section. For the most part[21] these patients are best treated conservatively as outlined and allowed to proceed to normal labor. Statistically the results have been shown to be much better than those attained by immediate cesarean section or interruption of the pregnancy.

Migraine

Migraine, in spite of our knowledge of genetics, vascular changes, and psychiatry, continues to be a baffling condition. In pregnancy there is often a decrease in the severity and frequency of the attacks, but this is not always the case. Sometimes patients have their first or most severe attacks during pregnancy. A patient of Dr. Lorne Macarthur illustrated this well.

Case 2.—A 25 year old woman was knitting at home, hopefully awaiting the onset of labor on October 3, 1954, when she developed a numbness in the right hand at 11 a.m. She then found she could not focus her eyes properly and became confused. Her husband said she spoke clearly, but he could not get the words. This was followed by a very severe headache. Neurologic examination that evening was normal. With a positive family history, a tentative diagnosis of migraine was made. She went into spontaneous labor, and the next morning she was delivered of a normal child. Two weeks after discharge she had a second attack. This time it started with scintillating scotoma; she could not read, she became confused, and the left side of the tongue and lips became numb. Spontaneously she described it "as if it had had a shot of Novocain." For ten to 15 minutes she could not speak, and she developed a severe unilateral headache. Since then she has had only one minor attack. With the shift of signs from one side to the other, the positive family history, and subsequent information from her mother that as a small girl she suffered from bilious attacks, it seemed clear that this was a case of migraine, in some way brought out by pregnancy.

My experience has been that most patients with migraine get some relief during pregnancy, but those who don't seem to have much more dramatic auras

than the usual patient. Ergotamine or dihydroergotamine are useful as therapeutic measures, and in the doses commonly used do not have an adverse or stimulating effect on the uterus.

Subarachnoid Hemorrhage

Spontaneous subarachnoid hemorrhage is a dramatic and controversial condition to treat at any time. In the patient approaching term, it is even more so. On March 23, 1954 I was confronted with such a problem.

Case 3.—A 34 year old woman was already known to me, since she was the mother of a hemiplegic child patient who had recovered from tuberculous meningitis. She had been admitted to the Montreal General Hospital because of sudden onset of severe occipital pain, which soon spread to the whole head. She was eight and a half months pregnant, and it was her third pregnancy. Examination revealed some weakness of the right side of the face around the mouth, difficulty naming objects, and neck stiffness. There were no other localizing signs. Lumbar puncture revealed grossly bloody fluid and a presumptive diagnosis of an aneurysm of the left middle cerebrum was made. She was very restless and had difficulty moving around in bed. After considerable deliberation we elected to do immediate cesarean section, to be followed by transfer to the Montreal Neurological Institute for arteriogram and possible surgery. She withstood the section well, the arteriogram did not reveal any abnormality, and she recovered uneventfully with conservative therapy.

Unfortunately not all patients with a subarachnoid hemorrhage during pregnancy do as well as this one. Walton[22] reviewed the problem and concluded that aneurysms do not occur any more often in pregnancy than in other people of the same age. Reference has been made to the effect of relaxin on the ligaments and fibrous tissue of the pelvis. One cannot help but ask whether there is a general change in the fibrous tissue elsewhere in the body, and in particular whether the wall of an aneurysm may also relax or become weaker.

Treatment also presents a problem. Too few cases have been reported to lay down any specific rules. Further, the improvement in arteriography and increasing success of the neurosurgeon in trapping aneurysms have changed the whole problem. In general, if the hemorrhage occurs during or close to labor, then cesarean section is probably the method of choice for delivery. While considering the problem, preparation should be made to do an immediate section in the event of sudden death of the mother. If the hemorrhage occurs early, the pregnancy should be allowed to go to term and treatment of the aneurysm decided on after arteriography. The type of delivery will depend on the clinical evaluation and the arteriogram.

Puerperal Hemiplegia

The problem of puerperal hemiplegia has been extremely well presented by Stevens.[23] The symptoms consist of sudden onset of headache, convulsions, hemiplegia, and coma appearing several hours or weeks after delivery in a previously normal woman free of heart disease or hypertension. Stevens and others[24–27] produced good evidence to show that the cause is cerebral venous thrombosis.

A good deal was written in the past about puerperal aphasia.[28] In most instances this is just another manifestation of cerebral venous thrombosis. Martin[24] felt that the cerebral lesion was an extention of a thrombotic process elsewhere in the body. Kendall[29] considered it to be a primary condition resulting from local vessel damage during labor, assisted by three factors in the blood of the postpartum patient conducive to

thrombosis: 1) the increase in thrombocytes, 2) the increase in plasma fibrinogen, and 3) the increased "stickiness" of the blood attributed to the presence of large numbers of newly formed cells released from the bone marrow. For the most part infection as a cause has been discounted. However, Dr. Claude Bertrand recently told me of two cases that went on to abscess formation after antibiotic therapy had been stopped. There can be little question that the increased coagulability of the blood plays an important part. What the precipitating factor is remains uncertain.

Treatment consists of anticonvulsants, antibiotics, and anticoagulants. One should point out that there is considerable disagreement about the anticoagulants. Some authors attribute success to this, whereas others such as Stevens report success without anticoagulants. Krayenbühl[30] has treated some patients with a large surgical decompression. In his cases it seemed to be a life saving procedure; however, the author prefers the conservative approach. Again therapy is an individual problem, success depending more on individual care and attention rather than any specific method used.

4. TRAUMATIC AND TOXIC CONDITIONS

King[3] has an excellent review of the anatomic background and the lesions of the lumbosacral plexus occurring during delivery. They usually occur where there is a large baby, some pelvic dystocia, or prolonged difficult delivery. There is usually severe pain in one or both legs associated with numbness or weakness. The signs depend on the part of the plexus involved. As a rule, there is a fairly rapid partial return of function, followed by a slow, limited improvement. Paralysis of other peripheral nerves may occur due to pressure during the anesthesia. Recovery is usually spontaneous; however, search should be made for contributing conditions such as diabetes or nutritional deficiency.

Ruptured intervertebral disks are said to occur more commonly during the terminal months of pregnancy or during labor due to relaxation of the spinous ligaments. In my own limited experience, these patients have responded well to conservative treatment after delivery, and operative intervention has not been necessary.

One condition that has been of great interest to the author is the so-called thoracic outlet syndrome. Patients complain of diffuse pain in the hands, usually worse when in bed and getting more severe as the pregnancy advances. It is a condition which must be related to postural changes and relaxation of ligaments in women anatomically predisposed. Some have been helped with vitamins and exercises to strengthen the shoulder girdle. However, for the most part they have dragged on until the end of pregnancy when recovery usually occurs. The condition is easily distinguished from a protruded cervical disk, chronic ulnar nerve neuropathy, or a carpal tunnel syndrome, but it is often difficult to say where the exact site of the pressure is located.

Spinal Anesthesia

Spinal anesthesia may be the cause of relatively minor and transient disability such as the postspinal drainage headache or very grave and permanent paralysis due to toxic demyelination of the spinal cord. Those familiar with this problem are aware how strongly Foster Kennedy felt about spinal anesthesia. He once wrote the author: "Indeed in read-

ing my paper in Atlantic City, I adlibbed my opinion that if no other general anesthetic was available, I would seek out an operator with the speed of the 18th century, and the 18th century anesthetic—whiskey and laudanum." It is worthy of note that in their paper of 1950, Kennedy, Effron, and Perry[31] reported three patients with grave permanent paralysis following the use of spinal anesthesia for cesarean section. The author personally takes a much more lenient attitude. Having seen so many babies suffer from anoxia secondary to too much predelivery sedation and general anesthetic, we must not be too dogmatic about the dangers of spinal anesthesia. For cesarean section the author prefers local anesthesia and light general anesthesia if necessary.

Low pressure or drainage headaches are common after spinal anesthesia used during labor. The leakage from the hole in the meninges is probably increased by the contractions, particularly in the second stage of labor. Patients generally respond to elevating the feet and lying in the prone position, but the latter is difficult due to sore full breasts or, in the case of cesarean section, to the abdominal wound. These headaches can be very severe, as illustrated by a patient who went on to develop bilateral sixth nerve weakness.

Case 4.—A woman was admitted to the Homeopathic Hospital in labor on August 10, 1950. She was 27 weeks pregnant. She was given a spinal anesthetic which was not entirely effective, and some general anesthetic was used. The baby was premature and died. As soon as the patient could remember, she had a headache and pain down her back. She said the aches were mostly in the back of the head, and she developed what was described as a muscular spasm of the head, neck, and shoulders. She said it felt like a vise. She could not raise her head, and she felt she was going to be paralyzed. She had no appetite. When she sat up, she felt that her whole head was going to blow off. She was discharged on the seventh day, but continued to suffer from severe pains in the head, especially when she first got up in the morning. At the same time she complained of stiff neck. On the ninth day after delivery she developed double vision, which rapidly got worse. Following this the pains in the head and neck improved, but the double vision persisted. She was readmitted on the 14th day post partum. At this time there were no abnormalities in the neurologic examination, except diplopia due to bilateral sixth nerve palsy. A lumbar puncture was done with a 22-gauge needle, with the patient in the sitting position. The initial pressure was 290 mm. of water, and there was a good exchange. Then 35 cc. of Elliot's solution was injected into the subarachnoid space. The final pressure was 450 mm. of water, which brought the level up to just above the nape of the neck. Unfortunately she did not have a headache before the injection started. However, the injections did not produce any unusual symptoms. She stated: "I think I feel better in a general way." On September 11 the diplopia was improved. When she looked at objects ten inches from her they were in focus without diplopia. She remained in the prone position with the feet elevated for five days, at the end of which time the diplopia had cleared completely.

There can be little question from the description of the headache, neck stiffness, nausea, and so on, that her trouble was due to drainage of the cerebrospinal fluid through the initial hole produced in the dura. The intracranial course of the sixth nerve is a long one, and it is very sensitive to changes in intracranial pressure. No doubt the low pressure and subsequent traction was the cause of the sixth nerve palsy. This was a complicated case, but subsequent events cannot be attributed directly to the effects of the spinal anesthetic. She developed an organized system of delusion, became very depressed, and finally required shock treatment for the psychosis.

5. TUMORS

Tumors of the brain present many problems during pregnancy. First, one must make the diagnosis. This must be distinguished from eclampsia, which is usually easy in the absence of albuminuria and other signs peculiar to toxemia. Then other causes of seizures, headache, visual disturbances, and paralysis must be excluded. The tumors may be primary, such as gliomas, the meningiomas, or others peculiar to the brain, or metastatic. Rand and Andler,[32] in their excellent review, point out that it is impossible to make any hard and fast rule for the care of the pregnant woman who has a brain tumor. Each case must be studied individually. However, they do suggest that in the case of a glioma, prompt operative intervention is indicated, whereas one can afford to wait with the more benign tumors. Because of the marked rise in intracranial pressure associated with straining and normal labor, cesarean section is advised as the method of choice for delivery.

A patient seen recently at the Montreal Neurological Institute illustrated many of the problems associated with a brain tumor in the pregnant woman.

Case 5.—A 33 year old woman was admitted first on June 1, 1954, six months pregnant, complaining of severe head pain, double vision, nasal bleeding, and impaired vision. Two years before she had had a mastectomy for carcinoma. Examination revealed severe papilledema. Roentgenograms demonstrated two nodules in the lung, and a ventriculogram showed a left frontal tumor. She was in a critical condition, and something had to be done soon. The pregnancy was not far enough advanced to deliver a viable baby, and so Dr. Arthur Elvidge performed a left frontal craniotomy and partially removed a large part of the tumor. In view of the known metastases, we decided against x-ray therapy, and she was soon discharged. All went well until the night of August 4, 1954, when the author was called because the patient was psychotic and chasing her husband with a knife. Because of fear for him and the other children, she was immediately readmitted. There had been the most remarkable growth of tumor in the wound, with nodules the size of a walnut outlining the old incision. After many consultations, cesarean section was done on August 7, and she was delivered of a boy with bilateral club feet, but otherwise healthy. She deteriorated rapidly and died one month later.

Considering the modern endocrine therapy for carcinoma of the breast, the author cannot see that it is right to allow a woman with such a condition, who already has a family, to go through with a pregnancy.

6. OTHER CONDITIONS

Epilepsy

We have all had patients with seizures occurring during pregnancy or the puerperium. They often occur at a dramatic time, the incident is impressed on our minds, and it is easy to develop the belief that seizures are more frequent and more severe during this period. Over the years the myth has grown that the epileptic has more seizures during pregnancy, defective children are likely to be born, and pregnancy should be avoided. Baptisti[33] found the literature was obscure and in 1938 reviewed the problem and reported on a study of 37 patients. He concluded that epilepsy had no appreciable effect on the course or termination of pregnancy. The most serious thing that can happen is to diagnose an unknown epileptic as eclampsia. This was illustrated by a patient who recently presented for the first time as an emergency at the Royal Victoria-Montreal Maternity Hospital. She had had a series of seizures, had marked facial changes of advanced pregnancy, and seemed confused. She did not have any edema and urine was normal. We were

asked to see her as a preliminary to inducing labor. To make a long story short, she was obviously a severe mentally retarded woman with seizures, who was not eclamptic, but who just did not know where she was. That night she went into labor spontaneously and delivered a normal child.

The author does not agree with King,[3] who stated that pregnancy should be discouraged when there is a definite family history of epilepsy. Like so many other problems in pregnancy, each case should be handled on its own merits. Judging from personal experience and from reading the literature, epilepsy alone is not an indication to interrupt pregnancy.

Multiple Sclerosis

It has been widely believed that pregnancy played a part in precipitating or aggravating multiple sclerosis. Many patients have had abortions or been sterilized or both, because they were known to have multiple sclerosis. Yet until recently there was no clear picture of just what relationship pregnancy bore to this disease. McAlpine, Compston, and Lumsden[34] recently reviewed their own series of 250 patients, as well as those of Müller[35] and Tillman.[36] In Müller's series there were 448 cases, with 133 childbirths among 97 women. He found 24 relapses in 133 pregnancy years (18 per cent) as compared to 703 relapses in 3,210 patient years (21.9 per cent) in all the women in the series. Tillman, in a study of 291 cases, concluded that pregnancy is not responsible for the onset of multiple sclerosis, and that the results suggest that the exacerbations during or following pregnancy may be coincidental. McAlpine and coworkers concluded that the longstanding view that pregnancy has a deleterious effect on multiple sclerosis must be modified considerably. They do suggest, however, that pregnancy should not be advised until two years have elapsed without fresh symptoms, and that the patient during and after pregnancy should have adequate periods of rest each day and freedom, as far as possible, from mental strain. For the most part patients should be allowed to go to term; however, one must consider the whole problem. Occasionally there will be justifiiable exceptions to this rule.

In the older literature optic neuritis and myelitis are described in considerable detail as separate entities. The tendency today would be to class these as manifestations of multiple sclerosis. Transverse myelitis or myelopathy, as suggested by Needles and Davison,[37] certainly does occur, but like multiple sclerosis the true etiology is not known. They suggested some unknown toxic factor.

Blindness has many causes from the retinal hemorrhages of toxemia, and the optic neuritis of multiple sclerosis back to the occipital lobe infarcts. The literature on this problem is well reviewed by Carpenter, Kava, and Plotkin.[38]

Myasthenia Gravis

In 1942 Veits, Schwab, and Brazier[39] reviewed the literature on the effect of pregnancy on the course of myasthenia gravis. They agreed with most authors that the effect of pregnancy was favorable. Generally, one can expect a remission to come on during the second or third trimester and last for three to six months after delivery. It is not unreasonable to suppose that the dramatic changes that occur in the endocrine glands and the secondary effects on me-

tabolism and tissue may be the cause of the remission, but it is not clear how this is brought about. Venning[4] suggests the matter can be clarified by hormone assays on pregnant women with myasthenia gravis. Therapeutic abortion has not been found necessary and is not advised, provided the patient can be kept under control with Prostigmin.

Nutritional Disorders

It is well known that in warmer climates pregnancy predisposes to certain nutritional disorders such as beriberi, pellagra, and polyneuritis. There are many contributing factors, and it is difficult to say what is the specific cause in any one patient. Even in the mononeuritides due to pressure, there is usually an additional nutritional factor. First, there is an increased vitamin requirement due to the raised metabolic rate, lactation, or the demands of the fetus. Then there may be a decreased vitamin intake due to an inadequate high carbohydrate diet, pernicious vomiting, or other gastrointestinal disturbance. There may also be a decreased absorption of vitamins related to lowered production of hydrochloric acid. Finally, there may be other endogenous or exogenous toxins, such as porphyria, metallic poisoning, diabetes, or others which may contribute to the production of mononeuritis or polyneuritis. Dr. Francis McNaughton had an unusual case of recurring polyneuritis after three successive pregnancies, which is worthy of report.

Case 6.—A 23 year old woman was admitted to the Montreal Neurological Institute on March 5, 1952, because of progressive weakness of the face, arms, and legs, blurring of vision, and weight loss. Three months earlier she had delivered a normal child, and two days later her symptoms began. Following two previous pregnancies she had had similar but much milder attacks which cleared within three months. On examination she presented as a thin woman in no distress, but she was unable to sit or stand. The hands were flexed limply and were flaccid. Vision was grossly impaired, and there was some facial weakness, generalized muscular atrophy, and absent deep reflexes. All sensory modalities were impaired. Spinal fluid protein was 20 mg. per cent, and on one occasion only there was a one plus positive qualitative porphyrin test. She was given oral and parenteral vitamin B preparation and slowly recovered.

The problem of polyneuritis during pregnancy and the puerperium is well reviewed by Spillane.[10] He had excellent opportunities to study these nutritional disorders in civilians and prisoners of war while serving in the tropics and far east during the last war. In Canada the condition is rare. Due to popular demand, obstetricians are almost forced to give their patients supplementary vitamins.

SUMMARY

To summarize an article which in itself is a summary would be redundant. Some of the neurologic conditions associated with pregnancy and present day views on therapy have been reviewed. Reference has been made to leading articles on each subject so that those interested can easily probe deeper. Although we try to make rules, it is emphasized that treatment should be on an individual basis, thoughtfully considered in the light of our knowledge of the patient and the disease.

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Neurologic Manifestations of Magnesium Depletion States

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THE NEUROLOGIC MANIFESTATIONS of magnesium depletion states in animals are well known, having been studied extensively in rats,[1,2,3] dogs,[4] and cattle.[5,6] Young rats maintained on a magnesium deficient diet soon (seven to ten days) develop signs of increased nervous system irritability characterized by convulsions which occur spontaneously or can be easily elicited by auditory stimuli such as a high pitched dog whistle or a doorbell. These seizures often begin as "running fits" and go on to severe tonic-clonic convulsions which may be fatal. Magnesium depleted rats also develop vasodilatation with marked hyperemia of the ears and paws. This hyperemia often disappears after two or three weeks, although the animals continue on a magnesium deficient diet, and it may return later or may be followed by a dermatitis. Dogs on a magnesium deficient diet present much the same picture as rats but with less reaction in the skin and more evidence of nutritional failure.

Magnesium depletion or low blood serum levels of magnesium occur spontaneously in cattle and appear to be responsible for three disease syndromes all very much alike as to signs and symptoms but brought on by different circumstances. These include grass tetany (staggers[7]), lactation tetany, and the milk syndrome in calves.[8] Grass tetany occurs when cattle are first turned out upon new pasture and consume large quantities of food high in nitrogen. The attendant changes in metabolism cause a lowering of serum magnesium, with general irritability and muscular twitching in mild cases and violent convulsions and death in severe cases. Though the diet is not really deficient in magnesium at this time, feeding magnesium sulfate relieves the symptoms. This same mechanism probably accounts for the seasonal lowering of serum magnesium levels in cattle which occurs in March, April, and May. Similar symptoms appear on rare occasions during lactation in cows, apparently due to excessive loss of magnesium in the milk.

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Symptoms of magnesium depletion appear in calves fed only milk, especially if they consume large amounts of milk and grow rapidly. Here again the metabolic demands appear to outrun the supply of dietary magnesium. This is known as the milk syndrome and suggests that a similar situation, as yet unrecognized clinically, might occur in human infants. Magnesium depletion in calves has recently been the subject of careful experimental study by Blaxter and Rook.[5,6] The complete symptom complex includes increased reflexes, apprehensive behavior, muscular tremor and twitching, peripheral neuritis, opisthotonus, ataxia, and finally severe tonic-clonic convulsions and death. Auditory stimuli do not precipitate convulsions in these animals. The apprehensive behavior reminds one of the patient bordering on delirium tremens.

MAGNESIUM DEPLETION IN MAN

Magnesium depletion in man has been studied sporadically for many years,[9-13] but its occurrence has not been widely recognized either clinically or on the basis of serum determinations. Now, with the wide spread use of the spectrophotometer for other clinical tests, reasonably satisfactory magnesium determinations should be available to many physicians. Until recently magnesium deficiency in man had been reported in association with severe renal disease, toxemia of pregnancy, or severe illness associated with malnutrition, and the main symptoms described were those of tremor, muscular twitchings, and convulsions. Reduced magnesium in the skin has been reported in cases of neurodermatitis,[14] but dermatitis has not been reported in human magnesium depletion states. Recently Flink and associates[15] summarized much of the literature on magnesium deficiency and reported 30 cases occurring in chronic alcoholics, most of whom showed some degree of mental confusion, delirium, and hallucinosis, as well as muscular tremor and convulsions. This finding of magnesium deficiency associated with a condition as common as chronic alcoholism, and the suggestion that mental as well as purely neurologic symptoms may be related to magnesium depletion, increase the clinical importance of this condition tremendously.

During the past year we have obtained serum magnesium levels on a large group of patients suffering from a variety of mental and neurologic disturbances. The only group which has consistently shown lowered serum magnesium has been the severe chronic alcoholic group, with symptoms including one or all of the following: tremor, delirium, hallucinosis, or convulsions. Although a small group was studied, our findings completely confirm those of Flink concerning the association of low serum magnesium with this condition. As in his cases, the most severe symptoms were associated with the lowest serum magnesium. Although not done by the same method,[16] our serum magnesium levels in normal people agree exactly with those of Flink. Normal serum magnesium is considered to be 1.9 mEq./L. Values down to 1.7 mEq./L. are not considered evidence of real deficiency. In most cases with definite symptoms serum magnesium was below 1.5 mEq./L. and very severe cases below 1.25 mEq./L.

REPORT OF CASES

Twelve cases of magnesium depletion state associated with chronic alcoholism

TABLE 1

TWELVE CASES OF MAGNESIUM DEFICIENCY IN CHRONIC ALCOHOLISM

Patients	*BE*	*CV*	*CJ*	*FN*	*FT*	*LA*	*LF*	*LW*	*MW*	*MJ*	*MC*	*SR*	*Totals*
Age	38	55	55	30	35	38	41	24	43	44	38	44	40
Sex	M	F	M	M	M	F	M	M	M	M	F	M	3F 9M
Tremor	X	X	X	X	X	X	X		X	X	X	X	11
Delirium	X		X	X		X			X	X	X	X	8
Hallucinosis	X		X	X				X	X			X	6
Cirrhosis	X	X		X								X	4
Convulsions											X	X	2
Magnesium mEq./L.	1.16	1.48	1.27	1.23	1.52	1.16	1.32	1.48	1.23	1.44	1.5	1.11	1.33

are summarized in table 1. All but one of these had serum magnesium of less than 1.5 mEq./L. on admission. Two cases are typical of this group.

Case 1.—A 33 year old man gave a history of rather heavy drinking for a period of 15 years. On July 26, 1954 he was admitted to another hospital complaining of vomiting and pain in the chest made worse by a cough and movement. His temperature was 102°F. and a diagnosis of lobar pneumonia was made. At that time he began to show symptoms of delirium tremens and during the next day or two became very disturbed. He was transferred to the University of Virginia Hospital on July 29, 1954.

Upon admission he was somewhat confused and restless but was cooperative and did not appear to be hallucinating. There was considerable tremor, especially in the hands. Chest x-ray was negative. Serum magnesium on admission was recorded as 1.5 mEq./L.

Later on the same day he was admitted, he developed hallucinations and delusions and became much more disturbed. Another serum magnesium level was determined and was reported as 1.23 mEq./L. During the next 12 hours he was treated with two infusions each containing 10 gm. of magnesium sulfate, and by the following morning his hallucinations and delusions had disappeared and he became well oriented and began to sleep and eat well. He continued without symptoms until his discharge on August 4, 1954. The magnesium serum levels resulting from his treatment are shown in figure 1. From this it can be seen that his serum magnesium had returned to a relatively low level before his discharge but despite this fact his symptoms had cleared and had not returned.

Case 2.—A 44 year old man noted swelling of the abdomen and both legs for about one week prior to his admission to the University of Virginia Hospital on September 10, 1954. Just before admission he was seen by his physician who noted that he was jaundiced and referred him for this reason. The patient gave a history of consuming large amounts of beer and whiskey for many years and on at least two previous occasions he had had convulsive seizures when he stopped drinking. Upon admission he was drowsy and had a mild tremor. The sclerae were icteric and there were numerous dilated veins over the upper arms and chest. The liver was quite large and a mild degree of ascites appeared to be present. Edema was not very marked. The spleen was not palpable and the remainder of the examination was not remarkable.

Laboratory studies on admission showed a urinalysis of 3 plus bilirubin and positive for

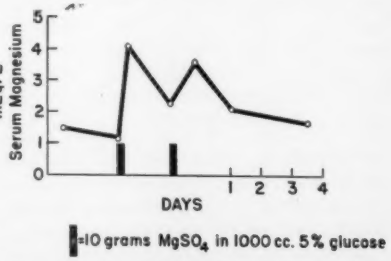

FIG. 1. Serum magnesium levels in a case treated with intravenous magnesium sulfate.

urobilinogen. Serum bilirubin was 4.0 mg. per cent. Prothrombin time was 16 seconds, with a control of 13 seconds. Hanger's flocculation was 4 plus.

On September 11, 1954 the patient had a generalized convulsion and became disturbed and disoriented. At this time a serum magnesium level was determined and showed 1.11 mEq./L. He was treated with 10 gm. of magnesium sulfate in 1000 cc. 5 per cent glucose, and the next morning his serum magnesium level was 1.80 mEq./L. He appeared somewhat improved that day and did not receive any further magnesium sulphate. As the day went on, however, he developed definite hallucinations and during the night these continued with severe tremor and apprehensiveness. The following day the patient was given another 10 gm. of magnesium sulfate intravenously with slight improvement, and on September 14 another infusion of 10 gm. of magnesium sulphate was followed by marked and continued improvements with disappearance of hallucinations, convulsions, and tremor. Magnesium level on the fifth day, with no previous infusion on that day, was 1.93 mEq./L.

It appears that this case responded to magnesium sulphate but that he did not receive enough magnesium sulfate to begin with, and he definitely became worse after it was not repeated on the second day.

We have studied two other especially interesting cases with symptoms related to low serum magnesium but not related to alcohol.

Case 3.—A 13 year old boy was admitted to the University of Virginia Hospital because of severe second and third degree burns received from electroshock which he suffered when he touched a high tension wire. The burns involved over 50 per cent of the body surface.

During a period of slightly more than one year in the hospital he developed many complications, including pyogenic arthritis of the elbows, severe osteoporosis, stag horn calculi of both kidneys, and urinary tract infection. As his renal and other complications became more severe, he often had elevated serum calcium as high as 14 or 15 mg. per cent.

After about 14 months of hospitalization he began to develop rather severe muscular twitchings, some signs of mental confusion, and disorientation. At this time the electroencephalogram showed some nonspecific abnormalities indicating mild diffuse brain change. Also at this point a blood magnesium was obtained and showed 1.23 mEq./L. Magnesium was given by intramuscular injection with definite relief of symptoms.

About a month later at a time when some muscular twitchings were present a serum magnesium was recorded as 1.93 mEq./L. At that same time the calcium was elevated. The patient eventually died with an elevated urea and generalized convulsions, which, however, were primarily terminal. Serum magnesium determinations were not obtained during the last month.

This patient was maintained most of the time on parenteral fluids and tube feedings. It would appear that the magnesium depletion was probably related to his renal disease, though at times his nutrition was very poor. On at least one occasion the muscular tremors were related to lowered serum magnesium and cleared when he was given magnesium. The possibility was raised that the imbalance of ratio between calcium and magnesium was enough to produce symptoms even when the serum magnesium was not below normal levels.

Case 4.—A 33 year old woman was admitted to the obstetric service on January 7, 1955 because of symptoms of pre-eclampsia and polyhydramnios. She was approximately at six and one-half months of her first pregnancy and had been hospitalized once before during her pregnancy for purposes of reducing her weight and stabilizing her condition.

Blood pressure was only mildly elevated, with the highest recording being 140/100. The urine showed a few casts and red cells although this varied from time to time, and at times the urine was completely clear. Urine albumin also varied from 0 to 2 plus. The patient had gained 16½ lb. in less than a month. There was 4 plus edema of the extremities and the abdomen was very much distended. Her weight was 143½ lb. She was put on a diet and given diuretics to reduce her weight, and she remained in the hospital until after the time of her delivery. During this time it was found that she had an extremely low serum calcium which varied from 4 to 6 mg. per cent. Also, it was found that the skull x-rays showed calcification in the basal ganglia and in the frontal region.

On the basis of these findings and lack of response to parathyroid hormone, a diagnosis of pseudohypoparathyroidism was made.

On Feburary 1, 1955 the patient became more mentally disturbed than before, very anxious and apprehensive, and apparently had some hallucinations and delusions. For this reason she was transferred to the psychiatric service where she remained for two weeks. During this time symptoms varied, but in general she was very apprehensive and at times had delusions concerning the death of her family. She had a mild tremor of the hands which was very noticeable when she tried to write. A serum magnesium done during this period showed 1.11 mEq./L. She had a generalized convulsion on March 27. Her child was delivered by cesarean section on March 30 without incident. She had another generalized convulsion on April 7. The patient's mental condition cleared up somewhat although she continued to be very apprehensive. Another blood magnesium done on April 20 was 1.29 mEq./L. At the time this was obtained the patient was not disoriented, had only mild tremor of the hands, but was rather apprehensive about her own future and at times expressed peculiar ideas about her family.

Further studies are planned concerning this patient's magnesium and calcium. This case is reported primarily because of the evident psychotic disturbances related to a proved low magnesium. Apparently these have varied and apparently when they were most severe the magnesium was very low in the serum.

We have seen a number of alcoholics who were either only acutely intoxicated with no chronic disease, or were already well over the immediate symptoms of alcohol withdrawal. In these the serum magnesium was often between 1.6 mEq./L. and 1.9 mEq./L. but was not markedly low. In one case admitted as an emergency because of convulsions, said to be associated with alcoholism, we were surprised to find an almost normal magnesium level of 1.80 mEq./L. Further investigation revealed a subarachnoid hemorrhage as the immediate cause of his convulsions.

TREATMENT WITH MAGNESIUM SULFATE

Most of these cases were treated with magnesium sulfate solution, 1 per cent in 5 per cent glucose, prepared by adding 20 cc. of 50 per cent sterile magnesium sulfate solution to an ordinary (1000 cc.) infusion. This was given intravenously over a one and one-half to two hour period. Most patients showed a rather rapid clearing of symptoms with this treatment, especially when they received two such infusions during the first 12 hours. No adequate controls were run on these cases, however, and complete proof of the value of magnesium sulfate in clearing alcoholic delirium must await more careful study. The use of intravenous magnesium appears safe if the following precautions are used. Deep reflexes should be present at the beginning, and if they become weak or disappear the infusion should be discontinued. Injectable calcium gluconate should always be at hand in case it is needed. Perhaps most important of all, magnesium should never be given to the patient until it is absolutely certain that kidney output is good. We have had only one untoward reaction, and it occurred in a patient who was dehydrated and practically anuric. Injection of calcium gluconate brought about complete recovery from signs of hypermagnesemia.

Magnesium sulfate can be given intramuscularly although the injections are rather painful. In most cases 4 to 10 cc. of 50 per cent solution given intramuscularly and repeated three times a day should be adequate. For more severe cases, especially when associated with active convulsions, the methods described by Pritchard[17] for use in patients with eclampsia could be used. This

consists of the intravenous injection of 4 gm. magnesium sulfate in 20 per cent solution given over a period of four to five minutes, to be followed immediately by an intramuscular injection of 10 gm. of magnesium sulfate as 50 per cent solution, half of the total volume in each buttock. Then 5 gm. of magnesium sulfate as a 50 per cent solution may be given intramuscularly every four hours for a period of 24 to 48 hours, unless the patellar reflex disappears or unless urine output were to drop below 100 ml. for four hours.

In recording serum magnesium levels in a large group of patients, we have found a few cases with low magnesium levels who did not show any of the usual signs and symptoms which were described above as associated with low serum magnesium, especially in alcoholics. Actually very few of these levels have been extremely low, but enough of them have been at 1.5 mEq./L. or below to indicate that factors other than low serum magnesium must play a part in this clinical syndrome. Cases in which we have recorded low serum magnesium include hereditary tremor, hyperthyroidism, epilepsy, pregnancy (toxemia?) depressive reactions, and renal disease.

Only in cases of hereditary tremor have we actually felt that the lowered serum magnesium was fairly consistent, and some of these have shown reduction of tremor when given magnesium intravenously. One typical case, however, did not respond at all. What, if anything, this means when coupled with the common observation that hereditary tremor is inhibited by the acute effects of alcohol and made worse by the withdrawal of alcohol, we do not know and have not yet been able to answer satisfactorily.

Serum magnesium levels have been low in some cases of epilepsy, but they have also been perfectly normal in most cases. The few cases with low serum magnesium have nearly all been of the hereditary or centrecephalic type of seizures. We have not been able to demonstrate any definite benefit from giving magnesium sulfate in these cases, even though we do not have a large well controlled series. It has been given intravenously, however, to several typical cases without any dramatic results. It would not seem that giving magnesium orally would prove much one way or the other, since we have shown in our laboratory that magnesium sulfate given orally has little or no effect on serum levels and that only a very small part of the oral dose is excreted in the urine (less than 2 per cent). This agrees with the recent findings of Pritchard[17] and contradicts prevous reports of a large per cent of oral magnesium sulfate absorbed into the body and excreted by the kidney.[9]

MECHANISM OF ACTIONS

The search for the basic mechanism of such neurologic conditions as convulsions or tremor, as well as mental conditions, such as psychoses, has become more and more centered in the field of nervous system metabolism and chemistry. The findings of a low serum magnesium associated with certain symptoms still leaves us far from the goal of step by step physiochemical understanding which we desire. Neither the site nor the method by which magnesium depletion produces symptoms is known. In the past, speculation has

leaned toward the concept that magnesium is important in a number of intracellular enzyme systems and depletion of the intracellular magnesium leads to derangement of functions and hence to the symptoms observed.

Extensive studies by Engbaek[18-20] concerning the action of magnesium on the nervous and neuromuscular systems indicate that the magnesium ion exerts its main influence at two sites, one upon the central or cellular portion of the neuron, and the other at the neuromuscular junction. An excess of magnesium decreases the amount of transmitter substance (acetylcholine) liberated at the end plate, thus acting in a fashion similar to curare. On the other hand, calcium increases the amount of transmitter substance liberated and directly antagonizes the effect of magnesium on the motor nerve endings.[20-22] It would appear from these facts that the tremor apparent in magnesium depletion state might well be the result of decreased magnesium acting on the neuromuscular junction, and any relief of tremor brought about by magnesium administration would be due to its peripheral effect.

The mechanism of central effect of magnesium is not nearly as clear as the peripheral effect. While there is no doubt that magnesium takes part in many important enzyme systems within the nerve cell,[23] there are a number of reasons why effects on these systems do not seem to adequately explain the clinical effect either of increased or decreased magnesium. First of all, the anesthetic action of increased magnesium levels is very rapidly counteracted by calcium. The action is so rapid that it seems quite unlikely the site of action lies within the cell and much more likely that the site of action lies at the cell surface. As far as low magnesium level or magnesium depletion states are concerned, recent studies by Blaxter and Rook,[5,6] on the tissue levels of magnesium and magnesium depleted calves showed that, whereas bone magnesium was reduced to one third of normal, there was actually no cellular depletion of magnesium in the brain or the soft tissues. As far as the brain is concerned, we have recently confirmed the findings in our laboratory that the brain content of magnesium has been found to remain constant or even become elevated in rats suffering from a markedly low seizure threshold as a result of severe magnesium depletion. This finding of normal or elevated cellular magnesium content in the brain in magnesium depletion states seems to make it unlikely that central nervous symptoms, such as convulsions, are due to direct interference with intracellular enzyme system, but it seems more likely that the symptoms of magnesium depletion come about as a result of low levels in the extracellular fluid spaces and as a result of a marked change in ratio between extracellular and intracellular magnesium. As far as convulsions are concerned this appears to be very much the same mechanism which is true for sodium, wherein increased intracellular sodium or decreased extracellular sodium brings about a lowering of seizure threshold.[24,25]

The fact that symptoms of magnesium depletion appear in animals growing rapidly or when they are consuming a diet high in nitrogen suggests that intracellular needs for magnesium may well be increased at these times and

take precedence over maintenance of normal serum magnesium levels. It is worth noting that the same situations, especially during periods of increased growth, are the ones in which man predisposes to exacerbations of seizure states, especially those of hereditary origin and of centrecephalic type.

The findings and speculations indicate the need and also the possible reward of improving therapy in certain conditions by continued investigation of the effects of magnesium and other electrolytes upon the nervous system.

SUMMARY

Magnesium depletion in animals produces general irritability, muscular tremor, vasodilatation, dermatitis, decreased growth and convulsions.

The manifestations of magnesium depletion in man as reflected by low serum magnesium levels include tremor, muscular twitching, delirium, hallucinosis, apprehensive behavior, and convulsions.

Twelve cases occurring in patients with chronic alcoholism are reported. In addition, a case associated with severe burns, parenteral fluid administration, osteoporosis, and renal disease, and one associated with pregnancy, renal disease, and pseudohypoparathyroidism are described. Serum magnesium levels below 1.5 mEq./L. were found in most cases with severe symptoms.

Treatment with magnesium sulfate given intravenously or intramuscularly is safe and appears to produce clinical improvement.

A review of possible mechanisms by which magnesium depletion produces symptoms suggests that a marked change in ratio between intracellular and extracellular magnesium levels may be at fault. It appears that in magnesium depletion states intracellular magnesium is normal or possibly increased though serum magnesium is decreased, and that this, rather than depletion of intracellular magnesium, is the basic defect.

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■ Which elements of the central gray matter are employed in the transmission of sensitive impressions? This difficult question has not yet received a positive solution; but it cannot be doubted, at least, that the transmission takes place by both cells and nerve fibres united together, and not by cells alone acting at a distance upon their neighbors. Most of the nerve-fibres of the roots of the spinal nerves, after having reached the gray matter, attach themselves to the nerve-cells, and, as has been well demonstrated by R. Wagner, and by Bidder, and several of his pupils, these cells communicate with others in such a way that two kinds of transmission are possible, one across the cord, and another towards or from the encephalon. But, besides the nerve-cells and their nervous fibrils of communication, there are, in the gray matter, several collections of longitudinal nerve-fibres, forming very minute white columns, surrounded by the gray substance. These white columns, first well described by Mr. Lockhart Clarke, and, after him, by Prof. Schoreder van der Kolk, cannot be considered as the only channels, in the gray matter, for the sensitive impressions or for the orders of the Will to muscles. The number of fibres they contain is too small for them to have these functions alone, but it is probable that they participate in it. Are they employed for a peculiar kind of sensitive impressions while the other impressions would be transmitted by nerve-cells and their communications? This is a question that experiments upon animals cannot solve.

C. E. Brown-Sequard in *Lectures on the Physiology and Pathology of the Central Nervous System*, published in 1860.

Clinical Trial of a New Anticonvulsant, SKF No. 2599

A Preliminary Report

J. Gordon Milichap, M.D., Louis S. Goodman, M.D. and Jack A. Madsen, B.S.*

IN THE TREATMENT OF EPILEPSY, the efficacy of currently employed anticonvulsant compounds is limited by their untoward side effects. Though serious toxicity is rare, administration of therapeutic doses of phenobarbital or primidone (Mysoline) frequently results in excessive sedation, and the effects of diphenylhydantoin (Dilantin) to cause cerebellar ataxia and gastric distress necessitate careful adjustment of the dose. In addition, the gingival hyperplasia induced by Dilantin is often troublesome, particularly in institutionalized patients.

With the introduction of Mysoline as an effective antiepileptic, one of us (L.S.G.) was encouraged to explore the effects of other congeneric chemicals in which the C = O group of the urea moiety was similarly reduced to CH_2. Prominent among these congeners was 5,5-diphenyl-tetrahydroglyoxaline-4-one (alternatively designated 5,5-diphenyl-4-imidazolidone), hereinafter called SKF No. 2599, which bears the same structural relation to Dilantin as Mysoline does to phenobarbital (figure 1).

Goodman and associates[1] have investigated the anticonvulsant activity of SKF No. 2599 in animals by a variety of electroshock and chemoshock seizure threshold and pattern tests. When compared with Dilantin in rats and mice, SKF No. 2599 is somewhat less potent but is much less toxic, and thus has a wider margin of safety. In cats the drug is as potent as Dilantin and its anticonvulsant action is more prolonged. In its ability to prevent maximal electroshock convulsions in rabbits, SKF No. 2599 is twice as potent as Dilantin. Particularly noteworthy is the fact that SKF No. 2599 can elevate the threshold for minimal a.c. electroshock seizures, whereas Dilantin is incapable of doing so in intact animals.

Moreover, subsequent studies in rats have shown that SKF No. 2599, quite unlike Dilantin, has little or no stimulat-

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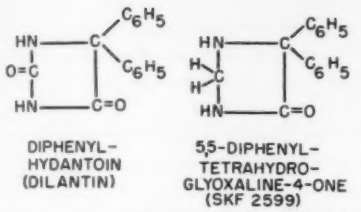

FIG. 1. Structural formulas of diphenylhydantoin (Dilantin) and SKF No. 2599.

ing effect on the adenohypophyseal-adrenocortical system. Criteria employed to measure the relative effects of the two drugs on this system included 1) ability to elevate electroshock seizure threshold in normal versus adrenalectomized animals, 2) ability to decrease adrenal ascorbic acid and thymus weight, 3) ability to increase the glycogen content of liver, muscle, and brain, and 4) effect on the blood concentration of corticosteroids.[2-4] The stress-like action of Dilantin to induce secretion of those adrenocortical hormones which render animals more susceptible to experimentally evoked convulsions accounts for the relative inability of the drug to elevate electroshock seizure threshold in animals.[2,3] It may also explain the hirsutism and perhaps the gingival hyperplasia observed in the course of Dilantin therapy in man. The influence of Dilantin and SKF No. 2599 on plasma 17-hydroxycorticoid levels in epileptic patients is discussed later in this report.

In addition, Goodman and associates[1] tested the effect of SKF No. 2599 on maximal seizures induced by therapeutic electroshock in psychiatric patients. The tonic component of the maximal seizure was prevented in six of the nine patients studied; in the remainder, the duration of the tonic phase was significantly decreased. Side effects were minimal in the doses employed. The ability of SKF No. 2599 to modify consistently these therapeutic major seizures in relatively nontoxic doses was unexpected, since the equieffective doses of conventional antiepileptic drugs are usually in the toxic range.[5]

In view of the apparent advantages of the compound, its clinical evaluation in epilepsy appeared warranted. The present preliminary report concerns a six-month trial in patients with drug-refractory epilepsy, carried out at the American Fork Training School and in the pediatric department of the Salt Lake County General Hospital, Utah.

CLINICAL DATA

Of 22 patients included in the trial, 20 were severely retarded mentally and ten had cerebral palsy. Their ages ranged from three to 31 years, with an average of 18 years. Twenty patients had grand mal (associated with psychomotor epilepsy in two) and two patients had psychomotor epilepsy alone.

The electroencephalograms obtained in ten patients were abnormal, and nine of these records showed seizure discharges. Among the abnormalities noted were focal slow spike-wave discharge, spike discharge, and amplitude asymmetry.

To provide a rigorous test of the drug, the patients selected were those whose seizures had proved refractory to treatment despite prolonged trial of conventional antiepileptic compounds. Average doses of Dilantin, alone or combined with phenobarbital, in 14 patients and of phenobarbital alone in six patients had failed to effect satisfactory control. The frequency of the seizures had been carefully recorded during the year prior to treatment with the new drug, and in

this control period the average monthly incidence of seizures per patient was eight.

Of the 14 patients taking Dilantin, 13 had developed gum hyperplasia which had necessitated total dental extractions in four cases and repeated oral surgery in two. In seven patients, hirsutism was present as a side effect of Dilantin.

TREATMENT AND DOSAGE

During the first two weeks of treatment with SKF No. 2599, an initial daily dose of 0.2 gm. was gradually increased to 0.6 or 0.8 gm. in divided doses, while all existing medication was gradually withdrawn. Eleven patients, however, had an exacerbation of seizures on this regimen; in three of these phenobarbital was reintroduced for a further one-week period, and in four patients with numerous and severe seizures a small dose of the barbiturate was continued throughout the trial. The daily dose of SKF No. 2599 was then further increased by 0.2 gm. at intervals of four weeks, up to a maximum of 1.4 gm., until the seizures were controlled or toxicity occurred. The average optimal daily dose was 0.8 gm. or, on the basis of body weight, 20 mg./kg.

Eighteen of the 22 patients were treated with SKF No. 2599 alone for an average period of 18 weeks. In five of these patients whose seizures were incompletely controlled with the maximum tolerated dose, the treatment was supplemented with phenobarbital during the latter part of the trial.

RESULTS

The degree of seizure control obtained with SKF No. 2599 and the number and percentage of patients whose epilepsy was benefited by the drug are shown in table 1. The percentage reduction in seizures was derived by comparing the incidence of seizures during the last month of therapy with the average monthly incidence during the control year preceding the trial.

The results of treatment were assessed separately in the 18 patients who were given the drug alone for an average period of 18 weeks. In eight of these patients (44 per cent) the epilepsy was controlled completely, and in four (22 per cent) a reduction in seizures of more than 75 per cent was obtained.

In the evaluation of the drug at the end of six months, of a total of 22 patients, four were included in whom treatment had been supplemented with

TABLE 1

EFFICACY OF SKF NO. 2599 IN THE CONTROL OF EPILEPSY

Control of Seizures	*Patients Treated with SKF No. 2599 Alone*		*Patients Treated with SKF No. 2599 Alone, or Combined with Phenobarbital*	
	No.	%	*No.*	%
100% reduction	8	44	12	55
75-99% reduction	4	22	6	27
50-74% reduction	4	22	2	9
< 50% or no reduction	2	12	2	9
Total No. of Patients	18	..	22	..

phenobarbital for the entire duration of the trial, and five were included to whom supplemental phenobarbital had been given only in the last two months. In 12 patients (55 per cent) the epilepsy was controlled completely, and in six (27 per cent) a reduction in seizures of more than 75 per cent was obtained. Partial control was effected in two patients (9 per cent); in two (9 per cent) control was slight or absent. In three of four patients with psychomotor epilepsy, seizures were reduced to less than 25 per cent of their former number.

TOXICITY

Since the majority of the patients were hospitalized and under observation, it was possible to increase the dose of the drug until the seizures were controlled or toxicity occurred. The side effects encountered in ten patients resembled those from Dilantin therapy in that the central nervous system and gastrointestinal tract were chiefly involved. The number of patients in which each of the various symptoms was noted was as follows: nystagmus, four; ataxia, four; incoordination, three; drowsiness, two; tremor, one; anorexia and vomiting, five; abdominal discomfort, one; gum hyperplasia, one. Skin rash or other allergic reaction did not occur. It is possible that certain subjective reactions were not reported by the mentally retarded patients.

The daily dose which elicited one or more side effects in these patients ranged from 0.8 to 1.4 gm., the average being 1.0 gm.; on reducing the dose by only 0.2 gm., relief from the side effects was almost invariably obtained. Evidence for a slowly developing cumulative effect of SKF No. 2599 was observed in the fact that, after an increase in dosage, both therapeutic and toxic effects were slow in appearance and were often delayed for two to three weeks.

When vomiting occurred, it was usually directly related to the dose of SKF No. 2599. Although it was controlled in one patient by administering the drug after meals, ordinarily a small reduction in total daily dosage was necessary. The mechanism of the drug-induced emesis has not been determined, but there are reasons for believing that it is not due to gastric irritation. For example, vomiting often did not appear until a relatively large dose of SKF No. 2599 had been given for two to three weeks. This observation is in contradistinction to the vomiting observed early after the initiation of treatment with comparable doses of Dilantin.

Blood examinations, including estimations of hemoglobin, white cells, and platelets, and tests for protein and reducing substance in the urine were performed at the beginning of the trial and then at monthly intervals. Neither anemia, leukopenia, nor thrombocytopenia developed during the course of treatment. In two patients a trace of protein was present in the urine, but this finding was transient and microscopic analyses were normal. Since transient abnormalities of the urine may occur following seizures in patients with grand mal, microscopic analyses were generally omitted.

GUM HYPERPLASIA

In nine patients the Dilantin-induced gum hyperplasia which was present at the onset of the trial varied in degree during treatment with SKF No. 2599; at six months it was somewhat increased in two patients, decreased in three, and unchanged in four. Since gingival hyper-

plasia may remain apparent for periods up to one year on withdrawal of Dilantin, the effect of SKF No. 2599 on the gums was difficult to assess in such patients. Of nine patients whose gums were normal at the beginning of treatment, one developed moderate gum hyperplasia after five months. In comparison with this relatively low incidence in patients treated with SKF No. 2599, three of four patients in the same institution who were placed on Dilantin therapy (300 mg. daily) developed this side effect within six to 11 weeks.

COMMENT

In this group of drug-refractory institutionalized patients, it is probable that the daily doses of SKF No. 2599 necessary for the optimal control of seizures were relatively large, and hence that the incidence of toxic effects was magnified. Many of the patients showed evidence of brain damage, and resistance to anticonvulsant drug therapy in such cases is to be expected. In patients with normal mentality and without severe brain lesions, it can reasonably be anticipated that doses smaller than those employed in this trial will be effective and that the incidence of toxicity may thereby be reduced.

In confirmation of our animal studies[2-4] mentioned in the introduction to this report, preliminary clinical studies, to be communicated in full elsewhere,[6] indicate that chronic Dilantin medication can increase the plasma 17-hydroxycorticoid concentration. In a small group of patients receiving Dilantin and exhibiting hirsutism and gingival hyperplasia, the corticoid levels were found to be far above the normal range. Neither phenobarbital nor SKF No. 2599 caused any such deviation from normal (7 to 15 microgm. per 100 ml.) in the concentration of plasma 17-hydroxycorticoids. Although the exact relationship of Dilantin-induced adrenocortical secretion to hirsutism and gum hyperplasia remains to be determined, the above preliminary observations suggest that SKF No. 2599 differs from Dilantin in that it does not stimulate such secretion.

To be accepted for general use, a new compound must do more than demonstrate a positive effect; it must prove superior to drugs of established value in the disorder concerned. Even though the previous trial of conventional antiepileptic compounds in the patients in this series could not be regarded as completely adequate, the majority had received average doses of Dilantin, alone or with phenobarbital, for prolonged periods and without practical benefit. Within six months, by adjusting the dose of SKF No. 2599 until the optimally effective level for each patient was obtained, seizures were well controlled in 18 (82 per cent) of the 22 patients treated. Furthermore, in comparison with patients treated with Dilantin, the incidence of gum hyperplasia in the present trial group was minimal and skin rash did not occur. Drowsiness, which often limits the efficacy of phenobarbital and Mysoline, was infrequent. That SKF No. 2599 has advantages over existing anticonvulsant compounds is suggested by this preliminary clinical evaluation, and a further more prolonged and extensive trial is recommended.

SUMMARY

A clinical trial of a new anticonvulsant, 5,5-diphenyl-tetrahydroglyoxaline-4-one (SKF No. 2599), has been continued for a period of six months in 22 patients with grand mal or psychomotor

seizures which were previously uncontrolled despite prolonged treatment with Dilantin and/or phenobarbital. The majority of patients were mentally retarded and 45 per cent had cerebral palsy.

The epilepsy was controlled completely in 12 (55 per cent) of the 22 patients, and a practical level of control was obtained in six (27 per cent). Among the patients whose seizures were well controlled, three had psychomotor epilepsy. The average optimal daily dose was 0.8 gm. (20 mg./kg.).

Side effects, which resembled those produced by Dilantin, involved the central nervous system and the gastrointestinal tract; the incidence of gum hyperplasia, however, was minimal.

Compared with existing anticonvulsant compounds, SKF No. 2599 has exhibited definite advantages in this preliminary clinical evaluation, and more extensive trial is recommended, particularly in noninstitutionalized epileptic patients.

The authors wish to thank Dr. James F. Bosma, Dr. Vernon F. Houston, and the nursing staff of the American Fork Training School for their assistance and cooperation.
We are indebted to the Smith, Kline & French Laboratories for generous supplies of the drug used in this study.

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■ As long as the animals live after the section of the posterior columns, hyperæsthesia continues to exist, except in the cases where reunion takes place between the two surfaces of the section; but hyperæsthesia is greater during the first week after the operation than it is after a month or many months.

Laying aside the curious fact of the existence of hyperæsthesia, a fact which is observed also in man, when the posterior columns of the spinal marrow are altered or injured, in a small part of their length, it results from the experiments consisting in a transverse section of these columns that the transmission of sensitive impressions to the encephalon does not take place only along the posterior columns. If a complete transverse section is made upon any part of the restiform bodies, sensibility becomes very much increased in every part of the limbs and trunk.

C. E. Brown-Sequard in *Lectures on the Physiology and Pathology of the Central Nervous System*, published in 1860.

Diffuse Leptomeningeal Carcinomatosis

Clinical and Pathologic Characteristics

Gerald O. Grain, M.D. and Jean P. Karr, M.D.

THE MANIFEST PURPOSE of cancerous invasion of the body is to accomplish death of the host by attacking vital organs. This objective is reached by diverse and devious ways. Invasion of the central nervous system by cancer is commonly seen in the form of blood-borne metastatic deposits in the brain parenchyma. A rapidly fatal result may occur, however, with a purely subarachnoid invasion of the leptomeninges and superficial cortical perivascular spaces, arriving by way of perineural channels in the cranial nerves and spinal nerve roots. The purpose of the present paper is to report two cases of leptomeningeal carcinomatosis with apparent lymph-borne invasion and to present clinical and pathologic characteristics which may more readily permit the recognition of this uncommon meningeal syndrome. Light may be shed also on questions involving perineural pathways and spinal fluid circulation, as well as the behavior of the cancer cell in the subarachnoid space.

Metastatic carcinoma of the central nervous system is not uncommon in the form of discrete nodular or focal deposits in the brain or as nodular infiltration of the dura mater. The rarity of diffuse carcinomatosis of the pia-arachnoid independent of blood-borne nodules is indicated by the infrequency of case reports on the condition. In the present review we are devoting ourselves chiefly to that group of diffuse leptomeningeal carcinomatosis in which autopsy has revealed no blood-borne metastatic nodules in the brain substance or in the choroid plexus or meninges, in order that we can more precisely establish the clinical picture of the uncomplicated condition and provide a strong argument for the lymph-borne mode of invasion of the subarachnoid space. Reference will be made to cases in which the two types of invasion may have coexisted, illustrating the difficulty in establishing proof of any one theory of invasion.

The literature on the subject totals about 100 cases, the number depending upon whether the various authors have enumerated only the pure leptomeningeal form without parenchymal or dural nodules, or whether cases with probable blood-borne metastases have also been counted. Some reports include cases of

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leptomeningeal sarcomatosis, which may present the same clinical picture and meningeal distribution, but which involves the possibility of primary meningeal instead of remote visceral origin and, therefore, do not belong in the present report. We have excluded all cases in which a pathologic examination of the central nervous system had not been made, but we have included cases in which the primary lesion had not been disclosed though the clinical and pathologic findings were otherwise reasonably complete.

A study of this condition reveals an obscure clinical picture and a unique form of malignant invasion. Many of the reports lack some detail of clinical or pathologic description, but even those studied and reported exhaustively give evidence of the difficulty of clinical and even of pathologic diagnosis. Our own two additional cases exemplify these difficulties.

CASE REPORTS

Case 1.—A 53 year old man was hospitalized on February 20, 1950 for severe headache and severe pain in the low back and legs of several weeks' duration. There was loss of weight, restlessness, evidence of pain, and marked rigidity of the neck and entire spine. There was no motor or sensory loss. The abdominal reflexes were absent. Patellar reflexes were at first increased, later absent. Percussion over the spine and sacrum produced clonic jerks of the trunk and lower limbs and a complaint of electric shock-like pain radiating into the legs. Signs of severe meningeal irritation dominated the entire course of this afebrile illness, which terminated in stupor, hyperpyrexia, and death after five months. The patient was mildly diabetic with fasting blood sugars ranging between 120 and 183 mg. per 100 cc. Exhaustive studies for a primary malignant lesion were negative.

Spinal puncture on seven occasions showed a moderate pleocytosis with elevated protein (table 1). No organisms were found by smear or culture. Myelography on March 5 revealed a defect at L3 on the right. This was repeated ten days later because of pain and atrophy in the right arm, and showed an irregular defect at C6 on the right. On April 1 a herniated cervical disk at C6-7 was removed by laminectomy with negative naked-eye findings in the meninges and cord. An electroencephalogram showed diffuse slow activity. Ventriculography revealed some dilatation of lateral ventricles with a slight shift to the left; the procedure was followed by coma and in three days by Cheyne-Stokes respirations and death.

At autopsy no primary malignancy was revealed until microscopic examination was made of a small suspicious area from the peribronchial region of the right lung hilus. A primary adenocarcinoma of mucous gland origin was identified. The tumor measured about 3 cm. in diameter. No metastases were found in other organs. The brain surface showed moderate

TABLE 1

CEREBROSPINAL FLUID FINDINGS, CASE I

Date	*Gross*	*Pressure mm.H_2O*	*Cells*	*Pandy*	*Protein mg./100*	*S mg./100*	*Cl.*	*Colloidal Gold*
2-24-50	Clear, colorless	180	7 wbc		146	78	680	0000112222
3-1-50	Clear, colorless	180	30 mono	++	120	72(129)*		
3-6-50	(Myelography)		21 mono	++	163			
3-22-50	Clear, yellowish	170	2 rbc	+++	325	48(116)		0000123110
3-30-50	(Myelography)		80 rbc	++	135	87(123)	520	
			50(pmn 40)					
4-24-50	Clear, yellowish	70	75 rbc	+	195	94(146)		0000122110
5-5-50	(Ventriculography)		2 pmn	+	300	92	590	

*Figures in parentheses are corresponding blood sugar values.

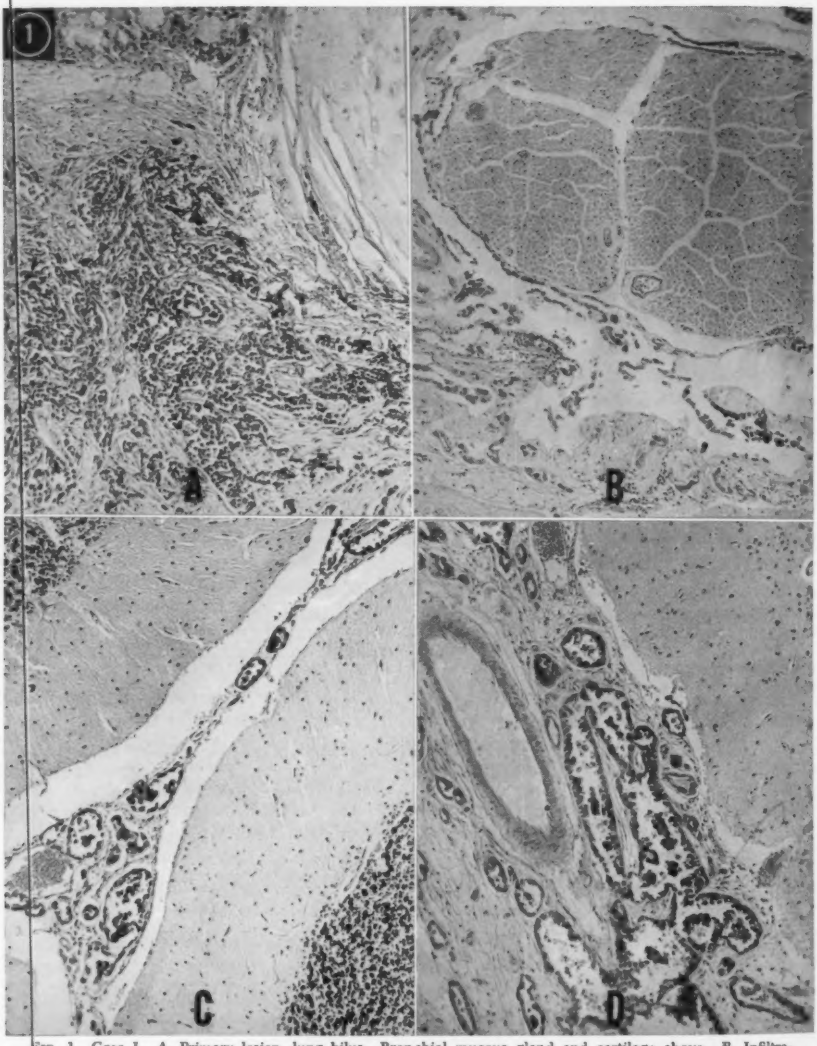

FIG. 1. *Case 1. A.* Primary lesion, lung hilus. Bronchial mucous gland and cartilage above. *B.* Infiltration about spinal cord (below) and nerve root. *C.* Cerebellar fissure. *D.* Cerebral sulcus. Hematoxylin and eosin stains.

congestion and slight yellowish opacity of the pia-arachnoid, particularly over the inferior surfaces of the temporal lobes. The spinal cord was grossly normal except for small, friable pink granulomata around nerve roots in the region of the lower half of the cord. Microscopic examinations yielded findings of diffuse infiltration of subarachnoid spaces of the brain and

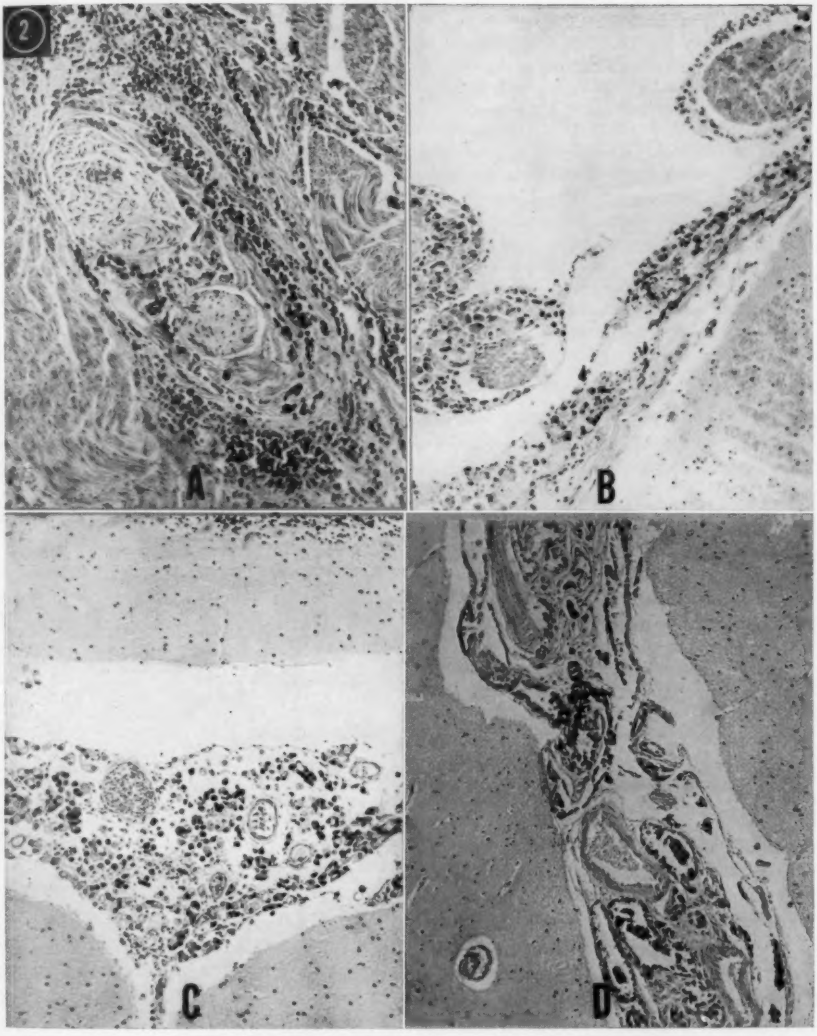

FIG. 2. *Case 2. A.* Perineural infiltration in stomach wall. *B.* Infiltration about spinal cord and nerve roots. *C.* Cerebellar fissure. *D.* Cerebral sulcus, frontal lobe. Hematoxylin and eosin stains.

spinal cord with carcinoma cells resembling those of the primary lesion (figure 1).

Case 2.—A 55 year old woman was admitted to the neurosurgical service on July 10, 1951 with a two month history of increasingly severe headaches, occasional dizziness, and vomiting. There were early bilateral choked disks, horizontal nystagmus, and absent abdominal reflexes.

An electroencephalogram showed a delta focus suggesting a deep right anterior cerebral or left posterior fossa lesion. Right carotid arteriography was normal. Ventriculography revealed a slight general ventricular enlargement and an enlarged choroid plexus of the left lateral ventricle. Suboccipital craniotomy demonstrated increased pressure, no tumor, and no ventricular obstruction. Ten days later the first lumbar puncture showed a normal pressure and yielded 36 red blood cells and 20 white blood cells per cu. mm. and 120 mg. of protein per 100 cc. The patient was discharged relieved of symptoms, but these later returned and were again improved after lumbar puncture, which yielded 220 red blood cells per cu. mm. and 76 mg. of protein per 100 cc. Vomiting, pain and stiffness of the neck, tinnitus, deafness, ataxia, and returning papilledema led to readmission on November 28 and to the discovery of a cord-like scalp induration near the suboccipital scar. This later extended to the skin of the right side of the neck. Pneumoencephalography showed ventricular enlargement without shift. Episodes of mental confusion, restlessness, and disorientation and the progressive development of ataxic gait, complete blindness, and deafness were followed by stupor, coma, and death nine months after the onset of headache.

Autopsy revealed adenocarcinoma of the stomach with metastases to the right lung, liver, pancreas, both adrenals, and to the skin of the right shoulder and neck. There was cystic dilatation of the choroid plexus, but there were no tumor nodules in the brain, choroid plexus, or meninges. Microscopic examination yielded findings of carcinomatous infiltration of the sheaths of nerves in the primary lesion of the stomach wall and of the leptomeninges of the spinal cord and brain (figure 2).

Pathologically both cases presented typical examples of diffuse leptomeningeal carcinomatosis without blood-borne metastatic nodules in the brain or meninges. The histology of the meningeal carcinomatosis reproduced that of the primary lesions. The signet-ring type of cell with eccentric nucleus was seen in both cases, particularly in the case of gastric origin. It is to be noted that in case 2 perineural infiltration was identified in the primary carcinoma invading the stomach wall.

REVIEW OF LITERATURE

Eberth[1] reported the first pathologic description of this condition in 1870, and Saenger[2] in 1900 reported two cases with pathologic confirmation in one. Most of the subsequent reports have detailed one or two cases. Siefert[3] in 1901 introduced the term meningitis carcinomatosa. Siefert's four cases all showed metastatic nodules in the brain, as well as diffuse infiltration of the pia-arachnoid, and he believed that the subarachnoid invasion was derived from involvement of pia by extension from parenchymal nodules near the cortex, as was undoubtedly the course of events in his cases. Saxer,[4] in the following year, presented the clinical findings of involvement of meninges and of cranial and spinal nerves, the somnolence of an encephalitis, and the gross and microscopic pathologic findings of primary gastric carcinoma and of pure leptomeningeal invasion.

In a case complicating primary carcinoma of the lung reported by Rehn[5] in 1906 there were no metastases in the brain, and the author suggested that the meningeal disease had arisen either by direct hemic metastasis or by extension from the cancerous pleura via perivascular lymphatics. In the same year Heyde and Curschmann[6] first described secondary propagation in the perivascular lymphatic spaces of the brain. In the absence of neoplastic nodules in the brain, they postulated probable invasion along lymph channels of intercostal nerves into the spinal canal.

In 1907 Marchand[7] described a case of gastric carcinoma with involvement of sacral nerve roots and infiltration of leptomeninges, and Knierim,[8] describing

the case more minutely in 1908, satisfied himself that the invasion could be traced continuously from the primary lesion in the stomach to the peritoneum and thence to perineural lymph spaces of the sciatic nerve and to the nerve roots. He believed this to be the pathway for invasion of the leptomeninges in the absence of metastatic nodules in the dura mater or brain substance. Heinemann reviewed 19 cases of meningitis carcinomatosa in the literature and agreed that either hemic or lymphatic modes of invision might occur.[9] In the same year Schwartz and Bertels[10] reported 11 cases, but included one case of dural metastases and one of sarcoma. Maass[11] described intense leptomeningeal infiltration by carcinoma derived from the ascending colon which he believed had extended along lumbar nerves from the peritoneal growth. Humbert and Alexieff[12] enumerated 23 cases in the literature and added one case with parenchymal nodules 2 cm. in diameter, which would eliminate the case from the lymph-borne series.

Bertrand and Aronson,[13] finding no visceral carcinoma, believed that their case was one of primary cancerous meningitis. More plausible is the belief that the choroid plexus can give rise to primary carcinoma. Kono[14] arrived at this conclusion in his case in spite of the presence of a probable hematogenous nodule in the choroid plexus of one lateral ventricle. A case described by Schuster[15] presented a typical picture of leptomeningeal carcinomatosis, apparently derived from malignant metaplasia of ependymal cells of the choroid plexus of the lateral ventricle. In several reports the choroid plexus had been involved by malignant deposit, and the usual assumption was that this represented a blood-borne metastatic lesion. However, some authors have suggested that invasion of the choroid plexus or ventricular ependyma in their own cases had resulted from extension of the subarachnoid involvement into the ventricles rather than the reverse, and therefore might still be considered primarily lymph-borne.

Morse,[16] reporting one case of cerebral metastases and another of leptomeningeal invasion without parenchymal lesions, expressed his belief in the perineural pathway of invasion in the latter type of case. Morse, like many others, described extensive infiltration into superficial layers of the cerebral and cerebellar cortex along perivascular spaces, and sometimes secondary formations of small, intracortical nodules arising from this perivascular infiltration. Lewis[17] in 1925 interpreted this latter finding in his case as an indication of extension of initially metastatic intracortical cancer to the meninges. Parker[18] interpreted minute cortical nodules as perivascular developments arising from subarachnoid involvement, and this interpretation is favored by most authors. He emphasized the latency of symptoms related to the primary lesion and the frequent early prominence of central nervous system symtoms. He and Cornwall[19] accepted the theory of perineural or "epineural lymph channel" invasion. Winkleman and Echels[20] included a typical case of leptomeningeal carcinomatosis in their discussion of metastatic carcinoma of the central nervous system, with reference to lymphatic channels as a valid pathway of invasion.

Krönig,[21] Siefert,[3] and Stadelmann[22] were among the early observers to re-

port tumor cells in the spinal fluid in meningitis carcinomatosa. Peter,[23] Lemierre and Boltanski,[24] and others emphasized the diagnostic value of this finding and the importance of careful cytologic examination of the centrifuged specimen.

Globus,[25] in discussing Weinberger's case in which tumor cells occupied capillaries of the choroid plexus, expressed the belief that the tumor cells in all these meningeal cases reached the brain by the blood stream and were then discharged by the choroid plexus into the cerebrospinal fluid. In 1942 Globus and Meltzer[26] again "found little evidence to support the existence" of lymphatic channels or their use for transportation of neoplastic cells to the central nervous system. They stated that their series of metastatic brain tumors contained four cases of initial spread to the meninges, but reported only one of these cases (case 3), however, and described another case (case 20) which showed perivascular but not subarachnoid infiltration. Alpers and Smith[27] in 1938 described a typical meningitic case and remarked that "the probabilities are that a metastasis localized to the spinal meninges is not accounted for by blood stream dissemination," but "by direct extension along the intercostal nerves to lymph spaces in the posterior roots and root ganglia, and . . . directly into the meninges." Hare and Schwarz[28] in 1939, reporting intracerebral carcinomatosis in 100 patients, found no case of meningeal carcinomatosis, but listed the several ways by which carcinoma may metastasize to the central nervous system and remarked that metastasis by the lymphatic route results usually in so-called meningitis carcinomatosa. Dixon, Kerr, and Sharp[29] presented a complete review of the subject.

The more recent publications on this topic include those of Madow and Alpers,[30] with four cases of the encephalitic type evidently resulting from predominant perivascular infiltration from relatively insignificant leptomeningeal invasion; the four cases of Dodge, Sayre, and Svien,[31] who emphasized the reduction of sugar content of the spinal fluid (which had been reported as early as 1905 by Scholz[32]); and finally the series of 18 cases (eight of them of the pure type) reported from the laboratory of Abner Wolf by Strange.[33] These more recent accessions to the literature are derived from the larger series of cases reported from the laboratories of neuropathologists. Unfortunately, in many instances the clinical aspects of these case reports are not as fully covered as the pathologic, and they do not lend themselves to the detailed analysis attempted in this paper for clarification of the syndrome.

It is recognized that cases of this condition come to the attention of pathologists more frequently than is reported. Doubtless many cases have been overlooked, either because they have not been clinically suspected or pathologically examined. Through clinical recognition of the condition one may avoid unnecessary antibiotic treatment for suspected tuberculous or luetic meningitis and unnecessary, usually fatal surgery for suspected brain tumor.

CLINICAL CHARACTERISTICS

We will attempt first to define the clinical picture found in the pure leptomeningeal form of the disease. By careful examination of case reports in

TABLE 2

CASES OF LEPTOMENINGEAL CARCINOMATOSIS GROUPED BY TYPES OF INVASION AND LISTED CHRONOLOGICALLY UNDER AUTHORS' NAMES

Group I.	*"Pure" or lymph-borne* (85 cases) Eberth, 1870. Saenger, 1901. Lilienfeld & Benda, 1901. Saxer, 1902. Scholz, 1905. Rehn, 1906. Heyde & Curschmann, 1906. Marchand & Knierim, 1907, 1908. McCarthy & Meyers, 1908. Stadelmann, 1908. Hoffmann, 1909. Lissauer, 1911. Schwarz & Bertels, 1911. Meyer, 1911. Beerman, 1912. Eickhorst, 1914. Pirie, 1920. Pette, 1922. Alsberg, 1923. Wüllenweber, 1923. Walshe, 1923. Peter, 1924. Moorehead & Wigham, 1926. Schlittler, 1926. Kino, 1926. Winkelmann & Echel, 1927. Cornwall, 1927. Penecke, 1927. Guttman, 1927. Gyarfas & Weiser, 1927. Lemierre & Boltanski, 1929. Selinsky, 1930. Meier, 1932. Bertha, 1935. Broderson, 1935. Alpers & Smith, 1938. Scheinker, 1939. DaCosta & Kernohan, 1941. Madeheim, 1941. Brunner, 1941. Schmidt, 1941. Globus & Meltzer, 1942. Allen & Mercer, 1942. Uspensky, 1943. Ardao, 1943. Floyd et al, 1944. Dixon, Kerr & Sharp, 1946. Willis, 1948. Madow & Alpers, 1951. Steiner, 1952. Dodge, Sayre & Svien, 1952. Strange, 1952. Meissner, 1953. Grain & Karr, 1953.
Group II.	*Blood-borne* (31 cases) Siefert, 1903. Peabody, 1907. Heimann, 1908. Heineman, 1911. Pachantoni, 1912. Maass, 1913. Humbert & Alexieff, 1913. Morse, 1923. Lewis, 1925. Parker, 1927. Szatmari, 1937. Weinberger, 1937. Meller, 1939. Schmidt, 1941. Duncan, 1941. King & Ford, 1942. Madow & Alpers, 1951. Dodge et al, 1952. Strange, 1952.
Group III.	*Choroid plexus, ependyma, pineal origin* (primary or metastatic) Bertrand & Aronson, 1921. Kono, 1924. Grage & Staemmler, 1927. Schuster, 1931. Gordin, 1933. Friedman & Plaut, 1935. Greenfield, 1938. Craig, Woltman & Kernohan, 1939. Da Costa & Kernohan, 1941. Hamrich & Hohl, 1948. Steiner, 1952.
Group IV.	*Dural origin* (illustrative cases) Westenhoffer, 1903. Lohe, 1911. Claude & Loyez, 1913. Albrecht, 1932. Vizioli, 1936. Bluhm, 1939.
Group V.	*Sarcoma*(?) (illustrative cases) Nonne, 1902. Rindfleisch, 1904. Hart, 1911. Haeger, 1911. Olivecrona, 1914. Boyd, 1925. Bailey, 1929, 1948. Kasinin & Crank, 1933.

the literature we have collected 85 cases, including our own two, in which there was no evidence of nodular involvement of the brain parenchyma or of malignant growth in the choroid plexus, ependyma, pineal gland, or dura mater. This series of cases must be considered to represent a true lymph-borne type of invasion (table 2, group I). One purpose in segregating this select group of leptomeningeal carcinomatosis was to determine whether certain characteristic clinical features might exist that would make it possible to distinguish the condition from metastatic brain tumor with or without meningeal invasion.

Clinically as well as pathologically, diffuse leptomeningeal carcinomatosis manifests itself as a chronic or subacute meningoencephalopathy. The symptoms and signs are produced by meningeal irritation, intracranial pressure, or neuronal dysfunction, either cerebral or spinal, or by combinations of these elements in different proportions and at different times. Meningeal irritation is almost always present in the form of neck rigidity and a positive Kernig or Brudzinski test, sometimes as girdle pain or limb pain. Cranial and spinal nerve involvement, with pains, paresthesias, palsies, and impaired reflexes, is often conspicuous. Ocular palsies are a frequent and often early complication. Paresis in a limb is rare even in mild degree. Tendon reflex hyperactivity,

when present, may be attributed to the effect of increased intracranial pressure or encephalopathy, or merely to meningeal irritation at spinal nerve roots. More commonly the deep reflexes are abolished, particularly late in the disease. Mental symptoms are described by all authors and in such terms as apathy, weakness, somnolence, lethargy, disorientation, impaired consciousness, defective attention and memory, confusion, stupor, coma, mutism, hallucinations, delirium, agitation, excitement, mania, and psychosis. Fluctuation in the degree of meningeal and cerebral signs has been observed during the progress of the disease. DaCosta and Kernohan[34] believed that the course of the disease proceeded by certain progressive clinical stages: 1) headache and occasional nausea and vomiting; 2) increase in headache associated with mental disturbances, beginning ocular palsies, and finally, meningeal irritation; 3) increase in all preceding symptoms, rapid increase in mental disturbances and in meningeal involvement, and death.

The sex of the patients in the series of 85 cases is stated in 79 cases, and of these 52 were males and 27 females. As will be seen, this marked difference in sex distribution has no apparent relationship to the organs primarily involved. The age at onset is given in 76 cases and ranged from 20 years (one case) to 73 years (two cases), with 58 cases, or 76 per cent, occurring between the ages of 30 and 59 years.

Of the 75 cases in which clinical findings were described with a certain amount of detail, initial symptoms included, in order of frequency, headache (46 cases), pain and/or rigidity of neck and back (30 cases), nausea and vomiting (25), cranial nerve (25), and mental symptoms (23 cases). The prominent objective findings in these cases can be grouped, in order of frequency, as meningeal signs in 70 cases, cerebral signs in 63 cases, cranial nerve signs in 51, and spinal nerve signs (root pain, sensory, motor or reflex defects, bladder dysfunction) in 37 cases. Eight cases showed a Babinski response at some stage. Fever, usually terminal, was mentioned in nine cases, but was stated to be absent in the majority of reports. In 21 cases there was some degree of papilledema. In 22 cases the spinal fluid pressure was reported as 200 mm. or higher, or simply as "increased."

A spinal fluid report was available in 65 cases. An increase in the number of cells of a non-specific type was reported in 28 cases. Large "mononuclear," "endothelial," "epithelial," or "strange large cells" were found in 18 cases and were identified as tumor cells in seven other cases. The protein content was increased above normal in 44 of the 48 cases in which it was reported. Sugar was less than 50 mg. per 100 cc. of spinal fluid in 15 of the 25 cases in which the sugar content was reported. Chlorides, when reported, were at a normal level.

The difficulty of clinical diagnosis is indicated by the infrequency with which an antemortem diagnosis was made. Dodge and co-workers[31] and Strange[33] each made the diagnosis clinically in two of their cases. The most common diagnoses in the series reviewed were tuberculous meningitis (nine cases), brain tumor (eight cases), metastatic brain tumor (eight cases), meningeal metastasis (seven cases), and meningitis, type undetermined (six cases).

The duration of life after onset of

symptoms attributed to the leptomeningeal invasion was less than three months in the majority of cases. It could be estimated in only 49 of the case reports. Eleven of the patients died in from three days to four weeks, 19 in from one to three months, eight in from three to six months, eight in from six to twelve months, and three after a twelve month period.

It is evident that the clinical manifestations of diffuse leptomeningeal carcinomatosis, apart from the signs of the primary neoplasm and its extracranial metastases (none of which may be manifest) are essentially those of meningopathy, cranial and spinal neuropathy, and encephalopathy, in that order of prominence. Signs of meningeal irritation, both by physical findings and spinal fluid changes, generally dominate the picture. Signs of involvement of cranial nerves and spinal nerve roots due to intense carcinomatous infiltration of these structures at meningeal levels, as well as signs of cerebral involvement by perivascular extension from the pia-arachnoid as a diffuse encephalopathy, may also be very conspicuous. Less than half the cases show any clinical sign of increased intracranial pressure. Clinical signs of focal brain disorder were rarely recorded. Electroencephalography and pneumoencephalography, when done, were usually noncontributory. The onset of the symptoms and signs is usually gradual and insidious.

These characteristics contrast with the clinical picture produced solely by cancinomatous nodules in the brain substance. Hare and Schwarz[28] found that the onset of intracranial symptoms was sudden in 36 of the 100 cases of cerebral metastases they reported, and could be called gradual in only 17 per cent. The age range was younger; 27 were under 40 years of age. Papilledema was seen in 31 per cent and blurring of optic disks in 40 per cent more. A convulsive seizure initiated the cerebral disease in 10 per cent. Focal signs were common and ictal onset simulated cerebral vascular occlusion in 78 per cent. There were clinical signs of either destruction or direct compression of brain substance in 68 per cent. Signs of direct cranial nerve involvement were rare. Meningeal irritation "evidenced by slight nuchal rigidity, subjective stiffness of cervical muscles, and severe headache" occurred in only 7 per cent of the cases. The spinal fluid showed increased pressure in seven of 18 cases; it yielded leukocytosis (predominantly lymphocytes) in seven of 54 cases, and protein values above 50 mg. per cent in 38 cases; sugar values were not given. Tumor cells are rarely discovered in these cases. Globus and Selinsky,[34] Globus and Meltzer,[26] and King and Ford,[35] have reported similar clinical characteristics for metastatic brain tumor. Baker[36] and Rupp[37] have also emphasized the prominence of focal cerebral signs in metastatic brain tumor, although Rupp reported a slow progressive onset in 31 of his 42 cases.

The probability, therefore, of an insidious onset and meningitic course in cases of diffuse carcinosis of the leptomeninges and of the more abrupt ictal onset in cases of nodular metastatic brain tumor, with signs of pressure and focal lesions but without meningeal irritation, permits some clinical differentiation of these two groups.

The clinical distinction between the

diffuse leptomeningeal carcinomatosis complicating cerebral metastasis and the pure meningeal case is less easily drawn, especially in those cases in which the parenchymal nodules are insignificant in number, size, and location. This group, in which at least one probable blood-borne nodule was present in brain tissue (table 2, group II), is separated from the pure leptomeningeal series on an arbitrary pathologic basis. The clinical findings present a meningoencephalitic picture which is quite indistinguishable for the two groups. The clinical symptoms and signs were predominantly meningeal and cerebral and of the same character as in those "pure" cases without intracerebral nodules. There were relatively more cases with sudden onset and with focal signs, but the numbers are too small to be significant. Papilledema and elevated spinal fluid pressure were no more common than in the pure group.

We have segregated another small but interesting group of cases in which typical clinical and pathologic pictures of diffuse leptomeningeal carcinomatosis were presented but which, in the presence of carcinoma of the choroid plexus, ependyma, tela choroidea, or pineal body, the possibility of blood-borne metastases to these structures could not be ruled out (table 2, group III). Clinically, the segregation of this group is probably not justified, since the findings reflect the meningeal involvement and the course follows that of an uncomplicated carcinomatous leptomeningeal infiltration.

In summary, a middle-aged patient with a chronic afebrile meningeal syndrome with general cerebral signs, and with or without cranial and spinal nerve palsies, pains or paresthesias, should be suspected of having diffuse leptomeningeal carcinomatosis. Typically, the spinal fluid will contain increased lymphocytes, increased protein, decreased sugar content, and no organisms. The finding of a primary carcinoma and of tumor cells in the spinal fluid would confirm the diagnosis.

PATHOLOGIC CHARACTERISTICS

The series under review as "pure" leptomeningeal carcinomatosis is identified more by pathologic than by clinical characteristics, since those cases in which there are small, indifferently located parenchymal nodules may present a similar clinical picture. Pathologically a basic difference in these two series is found in the predominance of primary gastric carcinoma in the uncomplicated leptomeningeal cases as compared with a predominant lung and breast origin in nodular brain metastasis. Of 81 cases of the uncomplicated series of 85 in which the primary lesion was located, 33 were in the stomach, 22 in the lung, 12 in the breast, and 14 in other organs. In the 31 cases complicated by blood-borne metastases the primary lesion was located in the lung in 14 cases, the breast in eight, the stomach in four, and in other organs in four. In the choroid ependymal metastatic cases the stomach and lung were equally represented with about four cases each.

A positive statement regarding metastases to other organs in the pure leptomeningeal group was obtained in only 42 of the 83 cases in which a complete autopsy was done. Of these the regional lymph nodes alone were involved in 11 cases. This contrasts with the high degree of metastatic involvement of

other organs or tissues in the blood-borne type of metastatic carcinoma of the brain.

Gross inspection of a brain with leptomeningeal carcinomatosis reveals no abnormality in a large number of cases. In 15 cases the brain was reported to be grossly normal. Among positive gross findings, flattening of convolutions was noted in four cases. Rarely the cerebrospinal fluid was noted to be cloudy or turbid. In 40 cases the leptomeninges were described as opaque or presenting opacities; this occurred as thickened areas in 16 cases or as diffuse thickening in seven cases. Other terms used were "opalescent," "cloudy," "milky," and "whitish areas." In these cases small "lentil-sized" or "hemp-sized nodules" were further described in such terms as "cell clusters," "clumps," "nests," or "localized thickenings." In the descriptions of microscopic findings in these cases, it becomes evident that these terms are applied to minute focal accumulations or local proliferations of cancer cells in the leptomeninges. There was no evidence that these carcinomatous cell clusters were of blood-borne origin.

The essential histologic finding of this disease is, by definition, diffuse carcinomatous infiltration of the pia-arachnoid and of all parts and prolongations of the subarachnoid spaces. This infiltration follows three fields of extension: the arachnoid and pia mater, the perivascular spaces of Virchow-Robin, and the periradicular sleeves of cranial nerves and spinal nerve roots. The two former are seen microscopically; the latter form is seen both microscopically and macroscopically as diffuse or nodular infiltration of intradural portions of the nerve roots. Occasionally, as in our case 1, this radicular involvement is found to have extended extradurally.

In the series of 85 cases, in addition to the diffuse carcinomatous infiltration of the pia-arachnoid and subarachnoid spaces in all cases, there was perivascular infiltration into the pia, subpial, or cortical tissue in 41 cases. In a few cases centripetal migration of cancer cells appeared to have taken place along pial septa, rarely in streams independently of pial prolongations, as in one of Steiner's cases[38] (figure 3). Usually, the infiltration has occupied the Virchow-Robin spaces for only a few millimeters from the pial surface, but in some cases there has been widespread perivascular involvement into deeper parenchyma. In our case 1 a minute perivascular cuff was found situated only a few millimeters from the wall of the fourth ventricle. In a number of cases the perivascular infiltration had undergone localized proliferation with

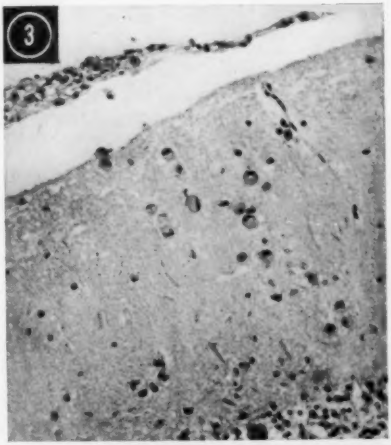

FIG. 3. Transpial invasion of cerebellum by signet-ring cancer cells. Hematoxylin and eosin stain. (Loaned by Dr. G. Steiner.)

formation of microscopic "nodules" within the brain substance. The lumens of the related small vessels contained no cancer cells, except in rare cases where there had been penetration of the vessel wall from the perivascular invasion, so that these perivascular nodules should not be considered blood-borne. In a few cases cancer cells were found on ventricle walls without infiltration of the ependyma.

Diffuse or nodular infiltration of cranial nerves was described in 13 cases. In the series as a whole no cranial nerve escaped involvement clinically, but pathologic evidence was often scanty. The spinal nerve roots, particularly the lumbar and sacral roots in the cauda equina, were found to be involved in 17 cases at autopsy. Although in several cases with heavy infiltration of the cauda equina a concomitant involvement of leptomeninges of the brain would suggest that the cauda had become secondarily seeded by sedimentation, there are some examples of exclusive involvement of the pia-arachnoid of the spinal cord and nerve roots. In no case of the series was the spinal cord found to be involved with intramedullary metastasis.

In at least eight cases the authors described perineural involvement at the primary lesion in the abdominal or thoracic viscus. These, including our case 2, were almost all of gastric origin. Da Costa and Kernohan,[34] mention that cancer cells were found in perineural and epineural spaces of the nerves at the primary site. Another finding which applied particularly to gastric cases was the signet-ring cell with eccentric nucleus and pale mucoid protoplasm. Of 14 cases in which this cell was described in the leptomeningeal infiltration, ten were of stomach origin, two of lung origin, and two undetermined.

The characteristic leptomeningeal invasion described in all these cases was that of a widespread filling of subarachnoid spaces with cancer cells, a carcinomatous invasion of the pia mater and arachnoid over the brain, the spinal cord or both, particularly about the vessels, and a varying degree of infiltration into superficial brain tissue along perivascular spaces. In all illustrations there is a remarkable similarity of this infiltrating leptomeningeal picture, although the richness of proliferation varies from a single-celled layer to heavy growth, sometimes in acinar formation. Secondary lymphocytic and polymorphonuclear infiltration was often described. Minor degrees of neuronal reaction were sometimes found, mainly in areas adjoining perivascular infiltrations into the brain substance. Secondary degenerations in the cord were also mentioned where posterior spinal roots and ganglia had been infiltrated.

In summary, the typical pathologic picture consists of diffuse carcinomatous infiltration of the pia-arachnoid of the brain and spinal cord with extension into arachnoid prolongations around cranial and spinal nerve roots and into perivascular spaces of the superficial cortex. The primary lesion is usually found in the stomach, lung, or breast. A search should be made for infiltration of cranial or spinal nerves in their peripheral courses, and particularly of the vagus and sympathetic nerves.

MODE OF INVASION

Since our main thesis is the support of the theory of perineural lymphatic in-

vasion in leptomeningeal carcinomatosis, we have been particularly interested in the views of the various contributors to the subject. Willis[39] has criticized the theory of perineural invasion chiefly because of the lack of evidence in the numerical sense. He states that "very few satisfactory examples of ascending cancerous invasion of the meninges will remain" after exclusion of metastatic tumors of the brain. He points out that neoplastic disease of the pia mater and arachnoid may arise in the following ways: 1) by dissemination from primary or from metastatic tumors of the central nervous system or dura mater; 2) by extension of abdominal or thoracic tumors through the intervertebral foramina (which would include perineural lymphatic invasion and perivascular lymphatic invasion); or 3) by "haemic embolic metastasis," that is to say, by blood-borne metastatic foci in the leptomeninges. He does state, however, that "occasionally cancerous permeation of the perineural lymphatics may be responsible for invasion of the spinal theca and meninges from abdominal and thoracic growths,"[40] but stresses that discrete nodules in the leptomeninges are seldom seen, even when blood-borne secondary growths are found in other tissues. He states that he has not seen a leptomeningeal growth which could be attributed to metastasis by the blood stream, yet shows uncertainty by concluding: "In some of the cases of diffuse meningeal carcinomatosis the tumor may have reached the meninges initially by the blood stream."[39]

Hassin[41] stated that the subdural and subarachnoid spaces may each become involved independently of the other by cancer cells reaching them by way of perineural spaces exposed to the primary lesion. The perineural invasion of the dura is extremely rare, and is usually of the blood-borne nodular type of origin. However, Burgstein[42] described cases of dural carcinoma apparently arising by direct spread from the thoracic cavity by way of perineural lymphatics. Morse[16] and Parker[18] both support the view of Hassin that the perineural invasion is initiated in peripheral cervical or cranial nerves by exposure to carcinomatous infiltration of cervical lymph nodes. However, the cases reviewed make little mention of cervical lymph node involvement. Steiner has recently reported the finding of involvement of sympathetic nerves in a case of leptomeningeal carcinomatosis.[38]

The acceptability of the perineural theory of invasion depends also upon the evidence for anatomic pathways which would permit such invasion. Commencing at the primary carcinoma, which exists in these cases chiefly in the stomach and the lung, the terminal fibers of vagus or sympathetic nerves may be seen in little bundles surrounded by cancer cells, all apparently within the lymph spaces surrounding the nerves (figure 2). These peripheral perineural lymph spaces can be seen in normal histologic preparations of these organs. The existence of spaces within the perineural sheaths of the nerves in their more central course is less easily proved, even though infiltration of the nerves by tumor cells has been well authenticated.

In 1764 Cotunnius[43] first demonstrated anatomically the presence of perineural spaces by air and mercury injections into the peripheral nerves. Sullivan and Mortensen[44] showed that intraneurally injected brominized oil will travel from the

sciatic nerve to the subarachnoid space in five or six hours. In 1948 French, Strain, and Jones[45] concluded that the channels called perineural spaces were simply tissue spaces in the connective tissue stroma of a nerve, were devoid of endothelial or mesothelial lining, and did not function in the normal circulation of cerebrospinal fluid. Final emergence of peripherally injected material into the subarachnoid space appeared to occur first by way of the subdural space and then by "break-through" across an arachnoid barrier into the subarachnoid space. In 1945 Chen,[46] though citing previous opinions that particulate matter did not normally ascend from endoneural and perineural spaces into the central nervous system but flows only in a centrifugal direction, showed evidence suggesting preformed spaces and a centripetal flow when the animal was moving about actively.

The ascending course of neurotropic infections of the central nervous system by peripheral nerve pathways depends upon propagation along individual nerve fibers and is unrelated to the question of ascent by perineural spaces. The controversy as to whether a centrifugal or centripetal flow of particulate matter such as carcinoma cells can occur is also somewhat irrelevant, as the extension from a primary malignant lesion centripetally along nerve bundles could depend upon rapid growth along lines of least resistance regardless of fluid currents. The question of a barrier to fluid communication from perineural space to subarachnoid space is also beside the point in regard to malignant propagation, which would readily invade the arachnoid cuff at the nerve roots and enter the subarachnoid space without resort to preformed spaces at this junction. Once the nerve root is reached, a centripetal propagation would require more definite antidromal powers, as it is accepted that cerebrospinal fluid is absorbed in the cul-de-sac of the arachnoid membrane around emerging cranial and spinal nerves apparently in a manner similar to the major flow from arachnoid villi to the superior sagittal sinus. Carcinoma cells entering the periradicular arachnoid sleeve would at this point, therefore, meet an opposing current.

The forces which influence the direction of spread of suspended matter in the subarachnoid space are generally considered to be the gradient of flow of the spinal fluid and the effect of gravity, with possible assistance by fluctuations of pressure resulting from respiratory movements and arterial pulsation. The direction of flow is from the choroid plexus of the ventricular system through the foramina of the fourth ventricle, the cisterna magna and other subarachnoid cisterns toward the absorptive areas, the arachnoid villi, and spinal nerve roots. Invasion of the subarachnoid space by carcinoma arriving by way of nerve roots and by ascent along the spinal subarachnoid space to the brain is, therefore, an example of antidromal course in which other forces besides fluid circulation and gravity play the major role. There is strong evidence, particularly in the reports of Dodge and co-workers[31] and Strange,[33] of a demand by the cancer cells for the carbohydrate metabolites present in the cerebrospinal fluid and of the depletion of glucose by the actively propagating carcinomatous growth. Probably when this depletion reaches exhaustion, the cancer cell fails to survive, the pure culture is no longer to be found

in the fluid obtained by lumbar puncture, and, as in some cases cited, the carcinomatous infiltration is discovered with difficulty in the pia-arachnoid but may be actively thriving in foci about cranial nerves or vessels, or in spaces of Virchow-Robin, where richer sources of metabolites may be found. Gravity may favor a heavy deposit of cancer cells in the basal cisterns and posterior aspect of the cord, and intracranial pressure may possibly contribute to migration into brain sulci and perivascular spaces, but there is evidence of activity as well as passivity in this cerebral invasion. There appears to be a migration toward the brain parenchyma by way of perivascular channels, and in some cases an attempt to invade the vessels or to strike inwards toward ventricles. It would seem that once launched in the perineural lymph channels, the cancer cell seeks one goal, the system of perivascular spaces of the pia-arachnoid and brain, where the fatal outcome is decided.

CONCLUSIONS

1. Carcinomatous infiltration of the leptomeninges may arise from metastases in the brain parenchyma, choroid plexus, pineal, and dura mater, and may originate from primary "carcinoma" of the choroid plexus, ependyma, or pineal gland.

2. A review of the literature reveals 85 cases of leptomeningeal carcinomatosis in which no metastatic nodules were found in the brain parenchyma, ventricles, or dura mater, and in which the choroid plexus was free from malignant growth. The stomach was the most common site of primary cancer. Two cases of this type are here reported.

3. The clinical and pathologic characteristics of this form of malignancy of the central nervous system are reviewed and defined.

4. The diagnostic value of the recovery of the cancer cell in the cerebrospinal fluid is emphasized. It is suggested that experimental material for in vivo or in vitro study of the vulnerability to metabolite or chemical changes in environment might be afforded by this source of the cancer cell.

5. In the absence of evidence of blood-borne invasion the probability of a perineural lymph-borne invasion is presumed, and this is supported by pathologic and experimental data derived from the literature.

6. The forces favoring ascending dissemination in the subarachnoid space and centripetal invasion along perivascular spaces in pial and subpial tissues are discussed.

7. An alert clinical suspicion for this complication of malignancy could lead to more complete pathologic demonstration of continuity of perineural invasion and portal of entry to the subarachnoid space.

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Neurologic Problems Encountered as a Result of Diving

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FOR CENTURIES man has subjected himself to stresses that exceed his physiologic controls. Deep sea diving is an example. Modern gas compression equipment has facilitated diving, but has also introduced new and interesting problems. Most of the problems are related to exposure to compressed air.

Exposure to increased barometric pressure increases the diffusion of gases across the alveolar membrane into the body fluids. The diffusion rate is proportional to gas solubility coefficients, blood-tissue perfusion factors, and to the differences in partial pressure.[1] A definite period of time is required to saturate the tissues,[2] but even when partial saturation exists, the exit of gas must take place slowly to prevent cavitation. When cavitation occurs, the resulting bubbles interfere with normal physiology by pressure or obstruction and produce signs and symptoms that constitute the clinical syndrome of "decompression sickness." The actual mechanism of symptom production is not established,[3] and there is doubt that the bubbles are totally responsible for the production of all neurologic signs and symptoms.[4] Safe passage from an atmosphere of compressed air to sea level is accomplished by the process of decompression.[5] When decompression is rapid, the situation of explosive decompression exists and is fatal without immediate recompression. Explosive decompression can occur if a diver overinflates his suit and "pops" to the surface, or when an aviator's pressurized cabin is accidentally ruptured. Fortunately, the aviator may return to the earth's surface automatically recompressing himself, but the diver needs to be recompressed in a treatment chamber. The rapid recompression accomplished seems to have some adverse effects upon the nervous system.[6]

Three problems seen in diving are of particular neurologic interest.

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EFFECTS OF HIGH PARTIAL PRESSURES OF CO_2

Many effects of carbon dioxide on the nervous system have been reported, but the specific mechanisms are not well understood. Carbon dioxide has its effect on the cells of the medullary respiratory centers because of its very high diffusion rate into the cells[7] where the intercellular alterations in pH are critical.[8] The rapidity of pH changes produced by the carbon dioxide make the cells appear particularly sensitive. Whether this is the sole mechanism of effect of carbon dioxide upon the nervous system has yet to be decided. Structural differences in carbon dioxide sensitivity have been reported.[9,10]

The physiologic effects of all gases are proportional to their partial pressures. The tolerance level of a gas is inversely proportional to its absolute pressure. It is imperative, then, that compressed air supplies be free of carbon dioxide. A slightly contaminated gas supply at sea level is lethal when compressed.

Low concentrations, 1 to 3 per cent, of carbon dioxide produce a stimulatory effect noted subjectively. During this period, motor skill and verbal skill test scores deteriorate.[11] Continued increase in carbon dioxide pressure results in mental confusion, altered sensorium, and eventual unconsciousness. When large partial pressures of carbon dioxide are given for short periods of time, as is done in carbon dioxide therapy for mental disease, seizure-like episodes occur.[12] Occasionally a deep sea diver will have a seizure-like episode under circumstances when it is believed that the carbon dioxide has increased accidentally. The toxic effect of oxygen cannot be ignored in these instances, however. Gyarfas, Pollock, and Stein[13] interpret the convulsive phenomena in humans during carbon dioxide therapy as corresponding to decerebrate seizures. They suggest a differential action of carbon dioxide, that of selectively depressing the cortical structures while not influencing or facilitating the subcortical structures. The mechanisms and the relationship to the diver's event at present are obscure.

Carbon dioxide inhibits convulsions due to electroshock and Metrazol. It augments seizures following methionine sulfoxamine, DDT, and oxygen under high pressure (OHP). As observed electrically, the inhibited seizures arise in the thalamus. When these seizures exist the administration of carbon dioxide will suppress the electrical seizure activity first in the cortex, then in the striatal, hypothalamic, and mesencephalic structures, and lastly in the thalamus.[14] The independence of cortical and subcortical activity in the response to carbon dioxide suggests that there are basic differences in the metabolism and physiology of these areas.

The biochemistry of carbon dioxide is also unclear. Tower[15] demonstrated that a biochemical lesion following methionine sulfoxamine occurs in the acetylcholine system and can be corrected in a positive sense with glutamine or asparagine. On the other hand, in preliminary clinical trials one patient with petit mal epilepsy was also improved with asparagine. Carbon dioxide would augment the methionine sulfoxamine lesion but would suppress the petit mal. This suggests that carbon dioxide and asparagine, at least, operate at different levels in the biochemistry of seizures.

OXYGEN TOXICITY

Bert[16] in 1878 first described oxygen toxicity, or poisoning, under high pres-

sures. For many years it has constituted a unique problem for deep sea divers. Pure oxygen under increased barometric pressures (OHP) in excess of 2 to 2.5 atmospheres absolute acts as a metabolic poison to the nervous system. Susceptibility is universal although there are daily individual variations in threshold.[17] Oxygen poisoning in humans produces one event clinically, a generalized seizure that may be preceded by several phenomena called prodromal signs. Their presence or existence is not constant even in one individual. Most common prodromal signs are nausea, headache, visual disturbances, fatigue, myoclonic spasms, and facial twitching.[17,18]

When any of these signs occur, a convulsion will usually follow if the partial pressure of oxygen is maintained. As long as the oxygen pressure is maintained, the convulsions will repeat themselves until the nervous system is exhausted and death occurs.[19] If oxygen pressure is reduced, the prodromal signs will disappear and no convulsion will occur.

Several interesting theories exist on the mechanism of OHP convulsions. Bert[16] suggested that OHP poisoned the enzyme systems to produce the hyperexcitability. Thiol enzyme systems in vitro are inhibited by OHP.[20–22] Unfortunately, three to seven hour exposures usually are necessary in vitro for inhibition, while at equal oxygen pressure in vivo convulsions occur in minutes. This difference must be explained. The various materials which protect the intact biologic system from the effects of OHP also are effective in vitro. A basic theoretical problem is to explain how inhibition of sulfhydryl-radical-containing enzyme systems could result in convulsions.

Some of the materials that afford protection against OHP also protect against radiation injury. A synergism between X-irradiation and OHP effects exists, if the times of the two exposures are closely approximated.[23] After a delay in excess of 18 hours, the X-irradiation then produces significant protection against OHP effects.[24] The terminal effects of massive irradiation are repeated seizures with final collapse. This effect is produced without irradiation of the head, suggesting a blood-borne toxin.[25] This indirect effect of radiation upon the nervous system permits one to speculate that, under conditions of OHP, the effect upon the nervous system may also be indirect.

NITROGEN NARCOSIS

This is the third problem of neurologic interest occurring in diving. Nitrogen and all the rare or inert gases possess many typical properties of anesthetic agents. Carpenter[26] determined the isonarcotic partial pressure for several inert gases, and concluded that the inert gas effects follow the Meyer-Overton hypothesis of anesthesia.[27] Other possible mechanisms of anesthetic effects must not be ignored.[28] The role of the dissolved gas in nonaqueous phases of myelin or lecithin in the interference of normal neural function has not been evaluated. The diver notices nitrogen narcosis at varying depths. Individuals lose their ability to concentrate, lose their sense of appropriateness, and become intellectually unreliable.[29] One story about this condition states that the diver cut his air hose and lifeline because they got in his way.

Narcosis may be the result of interference with the oxidative metabolism of the nervous system.[28] Studies on

pyruvate utilization in homogenates of brain and nerve[27] under nitrous oxide and cyclopropane show no change in pyruvate disappearance even after blockade of nerve conduction. Minimal changes in oxidative metabolism, however, might account for narcotic effects and yet not significantly influence pyruvate metabolism.

DISCUSSION

This brief description of three neurologic problems in diving and compressed air work suggest several areas of necessary research. The mechanisms of symptom production are not conclusively established in any of these problems. It is recognized that the high venous carbon dioxide pressure is related to the incidence of decompression sickness[30] and also to the incidence of oxygen toxicity, but the mechanism is not known.

The oxygen toxicity seen in compressed air work raises a considerable number of basic problems in neurophysiology. For many years it has been assumed that a generalized convulsion was a single event; the mechanism was identical from one seizure to the next. However, recent studies suggest that there may actually be many different mechanisms for the initiation of generalized convulsion, and that the only aspect of similarity is the final peripheral expression of the convulsion. Even the actual generalized seizure itself may be different, although each appears similar electrically. Since there are opposite effects from carbon dioxide on Metrazol-induced seizures and OHP-induced seizures, the study of oxygen toxicity requires more complete knowledge of the metabolism of a convulsion.

Inert gas narcosis suggests an entirely different series of problems. With the possible exception of the effects of hypoxia or anoxia on the activity of the nervous system, the depressant action seen with other materials is still a mystery. It is difficult to assume that depression of the general metabolism of the entire nervous system could be the sole mechanism, since recovery from anesthetic agents occurs at different rates. Quantitative studies of inert gas narcosis[31] have been done, and surgical anesthesia can be obtained with Xenon.[32] This indicates that the inert gases function anesthetically in relation to a physical property of the gas, and makes available a reasonable tool for research into the physical properties of nerve tissue. The problem of inert gas narcosis lends itself as an approach to anesthesia theory and from there to a possible understanding of the significance of the physical characteristics and qualities of our nervous system.

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Myasthenia Gravis

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IN 1934 the first great advance was made in the treatment of myasthenia gravis. On the basis of the observation that the symptoms of this disease resembled those of curare poisoning, physostigmine, known to be an antidote for the latter, was given to a patient with myasthenia gravis. Marked improvement in symptoms followed.

Over the past 15 years, various therapeutic methods have been employed for this disease. The treatment may be divided into two groups: 1) attempts to influence the course of the disease on a long term basis, and 2) investigation of drugs used symptomatically for immediate relief.

As for the first, thymectomy has probably been the most common treatment for myasthenia gravis. Operation has always been advised, of course, in patients with a mediastinal mass demonstrable by x-ray, as one would remove a tumor from any location, and some operations have been done where no thymoma existed. The results have been difficult to evaluate. Ordinarily one may say that a form of treatment which leaves so much doubt as to its efficacy is hardly a specific cure for the disease. It is interesting to speculate on the theory that any improvement in myasthenia with thymectomy may be an indifferent or shock effect of operation, and a study of a series of myasthenics who have had operations for other reasons or on other organs might be illuminating.

X-ray therapy has been almost as difficult to evaluate as thymectomy, but it seems to give results at least as good. Total dose irradiation was originally given, but for the past ten years we have been using courses of three treatments of 200 roentgens each, given on successive days to a total of 600 roentgens to the mediastinum. Irradiation is repeated at intervals of six months to one year, depending to some extent on the patient's progress. Early in our trial of small dose irradiation, complete remission of symptoms in one patient within one month of his first course of therapy encouraged further use of this simple, safe, and economically feasible measure. This patient, incidentally, is still in complete remission and has used no neostigmine for eight years. His examination today is entirely normal. As a control, other patients were given the same amount of irradiation to the spleen, and one of these patients experienced complete remission. Many patients have seemed to receive improvement within a month of the therapy, as might be expected if irradiation itself were the factor of

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importance in treatment. In the majority, however, the treatment cannot be shown to influence the course of the disorder.

An attempt is being made at present to evaluate a ten year study of the effect of irradiation, comparing the results on 100 patients with a group of nonirradiated controls. Only tentative conclusions can be drawn now, but it seems to us that the occasional improvement noted in irradiated patients justifies continued use of x-ray treatment, particularly when a patient is undergoing a relapse, increasing his medication, and still having progressively more severe symptoms. Under these circumstances we are glad to turn to any method which holds any promise of turning the tide of events. The variability of the course of myasthenia gravis and the occasional spontaneous remissions, of course, render the evaluation of patients most difficult, and results must be interpreted cautiously.

ACTH has had limited use in this clinic after our own initially disappointing results and after reports from other clinics of the posttreatment relapses which seem to be worse than the original status. The worsening of symptoms during ACTH administration makes it hazardous for the severe cases, and we have noted no really significant improvement to encourage its use.

The thyrotoxicosis which occurs so frequently in myasthenia gravis is now much less troublesome since the advent of the use of radioactive iodine. The diagnostic use of radio-iodine uptake is much easier for the patient and much more reliable in its results for the physician than is the basal metabolic rate. The therapeutic use of radio-iodine has eliminated concern about surgery in a thyrotoxic myasthenic patient.

Neostigmine produces its effect in myasthenia gravis by inhibiting the action of cholinesterase, preventing the hydrolysis of acetylcholine, thus allowing it to accumulate and cause its physiologic effect. Neostigmine has been used throughout the period of this study, and has always been the yardstick against which other forms of treatment have been judged. Chronologically speaking, the first anticholinesterase drugs used in this clinic experimentally as an adjunct to neostigmine were the organic phosphates. Diisopropylfluorophosphate or DFP was first given intramuscularly here in 1947. It proved to be disappointing, probably because we knew so little about how to use it. DFP was soon replaced by hexaethyltetraphosphate or HETP, which was then found to be effective when given orally. The active fraction in HETP, a mixture of phosphoric esters, was shown to be tetraethylpyrophosphate or TEPP, and the latter has been the most widely used in our series. For investigational purposes, however, we have given DFP, HETP, TEPP, and octymethylpyrophosphoramide, or OMPA by mouth at various times, and found that all are effective agents in increasing strength in myasthenic patients.

In our opinion TEPP has been the most useful organic phosphate. It has been administered orally as a 1 per cent solution in propylene glycol, usually in doses of 0.5 cc. measured in a tuberculin syringe by the patient. This dose is usually given two or three times daily and is taken in orange juice or the vehicle of the patient's choice. Since the anticholinesterase effect of TEPP is of long duration and therefore cumulative, the initiation of treatment requires either a higher daily dose the first two or three days to attain an effective level, or the slower method of giving the maintenance dose and waiting a week or two until the full effect is achieved. In this respect it is somewhat comparable to the digitalization of a cardiac patient. Some degree of cholinergic reaction consisting of salivation, nausea, vomiting, abdominal cramping, diarrhea, diaphoresis, and prostration are to be expected during the initiation of treatment with organic phosphates. Since patients must learn to recognize incipient reactions and to control them with atropine, careful instruction of the intelligent outpatient or preferably hospitalization with close observation, is essential. Eventually

most of the patients regulate themselves with 3 to 6 mg. of TEPP three times daily, with one or two 0.6 mg. atropine tablets taken with each dose of TEPP. Much of the original difficulty encountered with TEPP and other organic phosphates was due to the fact that neostigmine was withdrawn during phosphate therapy. It is true that neostigmine binds cholinesterase and therefore prevents the action of TEPP and cannot be given for at least two hours before a dose of TEPP, but it can nevertheless be given after the TEPP with a potentiated response.

It is obvious that many myasthenics are either not stable or intelligent enough to use a drug with such dangerous potentialities. Our series of patients treated with organic phosphate is, therefore, limited to 13, of whom five were males and eight females. The patients ranged in age from 19 to 63. They have been receiving organic phosphate as long as seven years. The small number of patients in our series depends partly on the dangers of TEPP therapy, the fact that the majority of our patients live at a distance from the clinic, and because we believe that only patients with severe myasthenia gravis require or justify the use of organic phosphates.

Two of the patients were definitely not improved. Eleven of the 13 patients considered TEPP therapy worth while and of their own desire continued its use. No patient had to discontinue TEPP because of side reactions alone. The two failures reported that TEPP therapy did not give them any better strength than neostigmine alone, and since the side reactions were proportionately greater they abandoned the use of the drug. Most patients experienced reactions at some time during therapy; these consisted of the usual parasympathomimetic effects of cholinergic drugs as well as the less frequently appreciated side effects of headache, cardiospasm, insomnia, and nightmares. However, as the experience of both patient and physician in administering TEPP increased, side effects were kept to a minimum and were readily relieved by adjusting the doses of TEPP and of atropine. The advantage of TEPP according to the patient's own evaluation is primarily due to its raising the base line of strength, thereby preventing the complete letdown of strength commonly experienced in myasthenics when their neostigmine dose begins to wear off. Thus it permits more restitution of strength by short rests and gives greater strength in the morning on arising. In addition, the action of each dose of neostigmine is potentiated, giving greater total strength, although some patients were maintained on TEPP alone without the additional use of neostigmine. The results indicate that while TEPP is desirable for its long duration of action, it does not usually benefit the major residual weaknesses which severe myasthenics have even when treated. In other words, the muscles that are not appreciably improved by neostigmine are not appreciably improved by TEPP.

In summary, it seems evident that TEPP at present deserves continued therapeutic use in the treatment of myasthenia gravis in selected patients.

Tensilon, a quaternary ammonium compound, is an interesting drug from an investigational point of view, because of its direct muscle-stimulating effect with only minor anticholinesterase action. However, it is of little clinical value in treatment except in myasthenic crises or as a diagnostic test for myasthenia because it is effective only for a few minutes when given intravenously and is ineffective when given by mouth. We prefer the use of neostigmine and atropine which give an opportunity for complete examination at various stages of the neostigmine effect. However, both tests are certainly valid and either may be used. Both compounds may cause mild transient increase in strength in normal or diseased muscles in patients who do not have myasthenia gravis, and this may lead to confusion in diagnosis if not evaluated carefully.

Mestinon is a homologue of neostigmine, known as pyridostigmine, and has been used

in the therapy of myasthenia gravis for several years. It has been studied in Europe but has not been well-known in this country until recently. Mestinon is supplied in a 60 mg. tablet which is approximately twice as strong as a 15 mg. neostigmine tablet. In other words, milligram for milligram, Mestinon is one half as potent as neostigmine, but it is only one fifth as toxic in its parasympathomimetic effects. Moreover, it has a longer duration of action than neostigmine, and in the 35 patients who have used it during the past year, it has been overwhelmingly preferred to neostigmine. In our series of 35 patients treated with Mestinon, only two preferred to remain on neostigmine. In general, the severe myasthenics needing many neostigmine tablets daily were more enthusiastic about Mestinon than were the milder myasthenics who took only three or four tablets of neostigmine each day. All patients found the duration of effect of Mestinon to be longer than that of neostigmine, and many reported that they were able to get up without help in the morning before taking their first dose of medication. The most important difference to most patients was the maintenance of strength on a more even level with improved endurance in contrast to their greater fatiguability and need to rest with neostigmine. To some patients the absence of cramps and diarrhea was the most important factor, and some even complained of constipation. Most of them required no atropine. Many were for the first time able to take adequate therapeutic doses because of the greater tclerance for the drug.

In only a few instances did Mestinon appear to actually eliminate the major residual weakness, whether ocular, bulbar, or peripheral, which was present on neostigmine therapy. In all of our patients receiving TEPP and neostigmine, Mestinon was substituted for neostigmine with no incompatibility. However, two patients found such marked benefits from the Mestinon that they felt that TEPP therapy was no longer necessary and therefore discontinued it. From our experience it can be concluded that Mestinon is a most valuable drug in the symptomatic treatment of myasthenia gravis, and in many patients it will supplant neostigmine altogether.

Recently we have been furnished another anticholinesterase compound as yet unnamed diethylaminoethyl oxamide 2-chlorobenzyl chloride (WIN 8077). It is five to ten times more active than neostigmine in anticholinesterase effect and has a duration of effect which is much more prolonged than that of neostigmine or Mestinon. However, its parasympathomimetic effect seems to be greater than that of Mestinon and the use of atropine is required by some of the patients. It is supplied in 25 mg. tablets. Eight patients are now taking this drug and comparing it with both neostigmine and Mestinon. Two of these patients prefer this new compound to Mestinon, but reports are not yet complete on other patients. One of our patients made the following comparison in the potency of the compounds. Originally she took from 30 to 60 tablets of neostigmine daily, in place of which she used 14 to 15 tablets of Mestinon. Now she uses two tablets of the new drug with better strength than she had with the previous drugs. Another patient said that he preferred it to either combined TEPP and neostigmine or Mestinon alone. It is much too early to draw definite conclusions about this medication, but it may be that it or other long lasting anticholinesterase drugs will have the advantage of TEPP without the powerful cumulative effect which makes TEPP dangerous.

In conclusion we may say that myasthenia gravis is still a grave disease, and that it is not always possible to prevent a fatal outcome even with all the forms of treatment now at hand. While the basic research on the primary etiologic factor is progressing, it is becoming increasingly possible to give more effective symptomatic relief to the myasthenic patient.

Mestinon is a product of Hoffmann-La Roche Company. WIN 8077 is a product of Winthrop-Stearns, Inc.

CLINICAL PATHOLOGIC CONFERENCE

E. P. Richardson, Jr., M.D. Section Editor

Presented by *J. Godwin Greenfield, M.D.,* Charles D. Aring, M.D.* and *Benjamin H. Landing, M.D.*

CASE PRESENTATION

A four year old white girl was hospitalized November 2, 1952 because of convulsions. She died about a year later.

The patient was born in October 1948. Delivery was uncomplicated. Early development appeared to be normal, but speech was delayed. She learned to say a few words, but never used phrases or sentences. There had been an attack of otitis media in April 1951. In September 1951 there occurred the onset of convulsive attacks, which appeared thereafter at fortnightly intervals. In these attacks she became pale, vomited, and lost consciousness, and there was jerking of all limbs and the eyeballs were rotated upward. Deep sleep followed. Preceding the attacks she was very quiet, stared, and then turned the eyes to the right. After about two months these manifestations were replaced by episodes of massive myoclonic jerking, in which she was usually thrown backward. Occasionally the contractions were localized to the head or to a limb. They occurred about 20 times daily. There were also times when she suddenly fell to her knees. Paradione and Dilantin reduced the frequency of the seizures. Walking deteriorated and by June 1952 the patient could neither walk nor sit up.

While hospitalized in August 1952 the patient was in a semicoma. She was aroused when anticonvulsants were replaced by Dexedrine, but the frequency of seizures increased markedly. All of the deep reflexes were maximal. Simple tapping of the muscles with the finger produced immediate and violent response. A light tap caused contraction of the limb touched, but heavier tapping evoked upward jerking of all four limbs. Pinching, stroking, and pinprick were without effect. A sudden sound caused generalized jerking. If the stimuli were repeated too rapidly, they lost their effect; 10 to 15 seconds were required between stimuli to evoke responses.

The patient was brought home, where the deterioration continued. Blindness and deafness supervened. When nourishment became a problem she was returned to the hospital November 2, 1952.

The patient was dehydrated and exhibited constant twitching. The skin was coarse, dry, and hairy. Vision was apparently limited to light. Primary optic atrophy was seen bilaterally. There was some retinal edema; the maculae were normal. The pupils reacted sluggishly to light. There were rolling movements of the eyes when she was aroused, but nystagmus was not observed. The jaw and sucking reflexes were very active and twitching of the tongue was noted. The neck was not stiff. Coarse rhonchi were heard throughout the lungs. The heart was normal. The abdomen and genitalia were normal. The deep reflexes were markedly exaggerated, and flexion response of the entire limb followed plantar stimulation as well as any stimulus to the legs, ankles, or feet.

Red blood cells numbered 4 million and the hemoglobin was 9 gm. per cent. Leukocytosis

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accompanied febrile episodes. The urine was normal and a phenylpyruvic acid test was negative. A liver profile was normal. The cerebrospinal fluid contained 8 mg. per cent of protein. The Wassermann test and gold curve were negative.

The electroencephalogram showed generalized irregular slowing of 1 to 4 per second, distorted by spike wave formations which appeared in all leads. A very high voltage negative spike appeared most frequently in the left occipital lead. On one occasion there was an electrical seizure of 4 minutes' duration. This started with slow spike wave formations, repeated at intervals of 1½ seconds. These were accompanied by 20 seconds of muscular tonicity, followed by slight irregular jerking movements. Then the whole cortex (except the occipital) participated in synchronous waves, 2 per second, with jagged contour of the background fast activity but without accompanying spikes. During the test there was some blinking and finally some twitching.

Roentgen study of the skull in November 1951 showed only decreased air cells in the right mastoid region. Pneumoencephalogram on April 9, 1952 was normal. A chest film on July 31, 1953 was normal.

There was little change in the patient's state during the year before death. Feeding was by tube during this period. Gastrostomy was performed April 28, 1953. Dilantin, Mesantoin, and various barbiturates were administered almost continuously. Contractures of the limbs developed. The patient survived two attacks of pneumonia. She left the hospital on September 23, 1953 and died at home three months later.

DIFFERENTIAL DIAGNOSIS

DR. CHARLES D. ARING: Undoubtedly this case presented knotty diagnostic problems during life, however straightforward the problem may now appear to us in the aggregate. She has had the prolonged period of observation that is sometimes required to make a reasonably accurate clinical neurologic diagnosis.

This little girl, who was kept alive until she was five years old, appears to have developed her disease sometime between the first and second year of life. The earliest hint that we get of trouble, according to the history given us, was in the delayed development of speech. Thus the earliest evidence of the disorder was picked up sometime in the first 15 months of life.

To the neurologist, this case is obviously one of what we call abiotrophy. Since neurologists are in the minority in this conference, we shall go to the authority who originated this term. Sir William Gowers[1] was one of the world's greatest clinical neurologists, and the scene of his operations was the National Hospital at Queen Square, a rather unique institution in that it was a cradle of neurology for the English-speaking countries as well as for many others. In February 1902 he delivered his lecture on abiotrophy which is so well known to neurologists. In it he said, "We do not apply the word death to slow decay of the elements; we speak of it as degeneration, but the process is in many cases, perhaps in most, an essential failure of vitality . . . I am met with the difficulty that we have no word by which to designate this conception — a degeneration or decay in consequence of a defect of vital endurance. I do not like new words — indeed, I dislike them — but if we have a conception for which no name exists, which we need frequently to speak of, it is not wise, I think, to shrink from an attempt to give it a name." As examples of abiotrophy, he cited the dystrophies as representative of muscle abiotrophy, and Freidreich's ataxia as an example of an abiotrophy within the nervous system, and Leber's disease as an optic abiotrophy. So by this term we mean a lack of vital force in nervous tissue — cells which seemingly have not been endowed with the capability of existing for a normal span.

As we look over this protocol we see that almost any category of nervous function was affected. Of mentality there is no indication that it ever developed. Speech was late and the child spoke only a few words. On the motor side, she exhibited profound disorders; there were weaknesses, tremors, seizures, and finally atrophy, paralysis, and this strange condition termed myoclonus. Concerning coordination we have no information from the protocol; we are not able to determine whether or not

the cerebellum was affected, although walking deteriorated and finally she could neither walk nor sit. But this was a terminal state which seems not to have supervened before the age of four and a half. So we have little or nothing in the way of evidence for cerebellar involvement, even though we might expect this part of the nervous system to show some change. On the sensory side, she was blind and deaf; she also had optic atrophy. On the reflex side, light and heavy tapping elicited responses that were quite abnormal and not unlike some of the spontaneous movements that are described. So, from the neurologic point of view, I believe that we have evidence of widespread abiotrophy of elements in the central nervous system.

Now what do we have to go through in the way of differential diagnosis to come up with a specific diagnosis for this little girl? If one thinks of the degenerative diseases of the nervous system in childhood – the abiotrophies – one might consider first those involving chiefly white matter, the various types of diffuse sclerosis that sometimes occur in childhood, or Schilder's disease. These would seem unlikely in our case for a number of reasons. Then there are the abiotrophies with selective degeneration of certain parts of the nervous system; there is a long list of neurologic conditions in which specific parts of the central nervous system are affected. Surely we must favor in this case the abiotrophies with universal cellular degeneration listed here; I will refer to them as the discussion proceeds.

These are particularly the disorders that are accompanied by abnormality in lipoid metabolism. The classic forms in which the disease is mostly limited to the central nervous system are the amaurotic idiocies. I have listed also the lipoidoses with a general disorder of lipoid metabolism with lesions in viscera; sometimes they also involve the central nervous system.

The reason I believe that this little girl's disease fits somewhere in the category of amaurotic idiocy is because we find good evidence of rather universal involvement of nerve cells. The protocol doesn't tell much – nothing as a matter of fact – about what stock this patient came from. We know there is contained in the literature the idea that the infantile form, the Warren-Tay-Sachs type of amaurotic idiocy, is seen mostly if not exclusively in Jews and particularly in Polish Jews. We have also no note about the family history; some of these conditions appear in families. We have a good description of the retina and optic nerve. Retinal edema is described, which of course is not what one hoped for, since if the patient had had the classical cherry-red spot in the macula, one could without doubt classify her in the infantile form of amaurotic idiocy. Variations in the appearance of the retina have been described. Dr. Greenfield has written a paper which shows that in the infantile forms of amaurotic idiocy, the lesion is particularly central in the fovea, and in the later forms, the lateral zones of the retina are more involved.

Abiotrophies with universal cellular degeneration (specific lipoid cell type)
- Infantile amaurotic idiocy (Warren-Tay-Sachs) onset 4 to 8 months
- Early juvenile or late infantile type (Bielschowsky) onset 3 to 4 years
- Juvenile type (Spielmeyer-Vogt) onset 3 to 10 years
- Late juvenile type (Kufs) onset 15 to 20 years

Disorders of lipoid metabolism sometimes including the central nervous system
- Nieman-Pick
- Hans-Schüller-Christian
- Gaucher
- Hurler's gargoylism

The phenomenon of myoclonus deserves a word because it was such a prominent feature in this patient. You will recall that this child had myoclonic movement, much of it seemingly spontaneous, some of it set off by stimuli of various sorts. This symptom is usually an indication of widespread neuronal damage. I think this would be corroborated by the electroencephalographic findings, where a rather diffuse electrical disorder seemingly reflected the diffuse cortical disorder that this child suffered. There

is some feeling that we need a new vocabulary for the phenomenon known as myoclonus. In many instances it has nothing to do with clonus, which is a term indicating repetitive movement, although these movements may assume this form, particularly in patients with amaurotic idiocy. Usually they are the result of contractions of small parts of muscles, and sometimes no gross movement occurs. In other instances of myoclonus, the patient may fall to the ground without any apparent movement of muscles except those that are involved in falling. This condition, myoclonus, has been described in all sorts of disorders, in acute and chronic encephalitis, in focal vascular or neoplastic lesions, and in the degenerative conditions, particularly those that I have listed above.

I believe that we may come to the diagnosis of amaurotic idiocy or central nervous system lipoidosis. Into which of these conditions should she be classified? This child's age of onset was seemingly somewhere between those listed for the infantile and early juvenile types, and she lived rather longer than would have been expected of a patient with the Warren-Tay-Sachs type. She did not have the clinical changes in the retina which would confirm a diagnosis of infantile amaurotic idiocy. So I would suppose that the evidence favors one of the later types of amaurotic idiocy.

DR. A. ASHLEY WEECH: Dr. Aring intimated that he was going to say a little more about why he thought this case did not belong in the group of degenerations of the white matter.

DR. ARING: I don't believe I've ever seen or heard of convulsive manifestations such as were suffered by this child in Schilder's disease; myoclonus would be unusual in Schilder's disease. Also this girl lived rather longer in active stage of her disease than one would expect. I should think that if she had had Schilder's disease, she should have been dead within a short time after the inception of her difficulties. She had much evidence of neuronal disturbance, particularly the convulsive manifestations. There was nothing abnormal in the cerebrospinal fluid, but the cerebrospinal fluid might be normal in either condition; however, Schilder's disease would be the more likely to be reflected in the cerebrospinal fluid.

PATHOLOGIC DISCUSSION

DR. BENJAMIN H. LANDING: At autopsy this patient was well developed and nourished. Externally she had a strikingly distended abdomen. She had flexion position of the extremities; since she had not been in the hospital during her terminal period, we were not sure how much of this could have been flexion deformity and how much was just a flexion position with rigor. The gums were extremely hypertrophic and I imagine she had been on Dilantin for some time, more recently than was implied in the protocol.

Internally there was a strikingly distended colon. This may have been an acquired aganglionic megacolon rather than the usual congenital form. The heart was somewhat enlarged and showed left ventricular hypertrophy and intimal fibrosis of coronary arteries, which was thought to be early atheroma because atheromata were visible in the aorta. I don't know whether she had hypertension; I think it's possible, with a diffuse neuronal disorder such as Dr. Aring postulated, that she could have had hypertension. She showed chronic pneumonitis, bronchitis, esophagitis, cystitis, and vaginitis, all findings which we find commonly in patients who have had poorly functioning nervous systems. Acute bronchitis appeared to be the cause of death.

The brain was grossly atrophic and weighed 540 gm., approximately half of normal size for a girl of her age. It had a distinct brownish hue, not entirely due to fixation. One could see the cerebral atrophy with narrow, rather pointed gyri between distinctly wide sulci. The folia were narrow and more widely separated than normal. The cerebral atrophy with wide-

ning of sulci was not so striking at the base as it was on the superior surface, although one could see it quite well in the orbital surfaces of the frontal lobes. A series of cross sections of the brain showed distinct ventricular dilatation and a decrease in width of the gray matter much more obvious than any decrease in white matter. The basal nuclei appeared a bit small; they did not appear to be as strikingly affected as the outer cortical gray matter. The brain was relatively firm in all areas, as was the spinal cord. The spinal cord showed relatively poor demarcation of the gray and white matter on section.

Microscopically, the brain showed three basic features: 1) myelin destruction and loss, particularly in the cerebrum; 2) loss of cells, most striking in the cerebellum where the granular layer was grossly depleted in cells in most areas; and 3) a decrease in the Purkinje cells. In other areas of the brain an alteration in number of cells was not so striking as the alteration in the appearance of the cells themselves. A section of the medulla showed many hyalinized and relatively swollen cells. With a higher magnification, one could see that the cytoplasm and nucleus in these cells were pushed to one side and a large, rather pale, hyaline, finely granular mass filled up the cytoplasm. In many of the cells this looked brittle and showed cracking.

In trying to fit this disease into the classification of degenerative disease of ganglion cells which Dr. Aring has proposed, one asks, what is this intracytoplasmic mass chemically? A thin rim of cytoplasm containing apparently residual Nissl substance surrounded the mass in each cell, proving it to be intracellular. This change occurred in all areas of the central and peripheral nervous system; it was present in the myenteric plexus and in sympathetic ganglia. It should have been possible to make a diagnosis if a biopsy of the gastric wall had been taken at the time of gastrostomy. The possibility of making a diagnosis of disease of this type should be kept in mind at operative procedures.

Sudan IV stain for lipid done on paraffin sections after formalin fixation indicated a general myelin-like nature of the intracytoplasmic masses. The myelins in general become relatively fat-insoluble after formalin fixation and are preserved in the paraffin sections. In the olives the cells were generally quite hyaline; in the motor nuclei the residual cytoplasm appeared normal. With Sudan black the staining of the myelin in the background was more sharp. So the material was presumably a lipoprotein, in the general myelin group chemically.

The Schiff stain for carbohydrate components showed that the masses were positive; sphingomyelin will give such a reaction; so will gangliosides, which contain carbohydrate residues. With the phosphomolybdic acid-stannous chloride stain, which theoretically stains choline, these cells are brought out quite clearly. This may indicate that they contain a phospholipid with a component of choline like sphingomyelin or some other glycolipid with a choline residue. Another slide was stained with crystal violet, which is ordinarily used as a stain for amyloid. There is a condition known as myoclonus epilepsy with amyloid degeneration of the ganglion cells. However, although the masses stained with crystal violet, they did not stain in the color which amyloid does, namely metachromatic. We interpret this as not indicating amyloid, but simply that many of these lipids will stain with basic dyes.

So we interpret this case as falling into the group of lipid degenerations of the ganglion cells. There were no abnormal features of the viscera, eliminating the Hurler and Niemann-Pick groups. According to Ford's[2] description of the amaurotic idiocies, the peculiar feature of the Bielschowsky group is that convulsions appear clinically before blindness, as appears to have been true in this case, as opposed to the Spielmeyer-Vogt and Tay-Sachs forms where blindness is usually one of the earlier clinical manifestations. It is our opinion

that this case falls into the Bielschowsky group of amaurotic idiocy.

The Niemann-Pick disorder falls into the same general group as the amaurotic idiocies histochemically; Hurler's syndrome also demonstrates approximately the same histochemical features as the Bielschowsky and Spielmeyer-Vogt amaurotic idiocies. Whether they are as similar chemically as they appear to be histochemically, I don't think we know as yet, and we are not in a position to argue that they are all variants of the same basic disease.

DIAGNOSES

Service diagnosis: Congenital degenerative disease of the central nervous system of undetermined type.

Dr. Aring's diagnosis: Amaurotic idiocy of the Bielschowsky type (late infantile).

Pathologic diagnosis: Amaurotic idiocy of the Bielschowsky type; acute bronchitis; chronic pneumonitis, bronchitis, esophagitis, cystitis, and vaginitis.

COMMENT

DR. J. GODWIN GREENFIELD: Bielschowsky emphasized the degeneration of the cerebellum in this condition. It is a very remarkable degeneration because it is one of the few conditions in which the granule cells fall out and disappear before the Purkinje cells. As you know, the Purkinje cells are very much more sensitive to anoxia, ischemia, and a great many other conditions than granule cells, but in this condition they are relatively preserved. There is one other condition which has recently been described in which the granule cells disappear, and that is poisoning with some of the mercuric methyl compounds used for preservation of seeds. There is a recent paper on this published from the London Hospital,[3] which showed a picture very much like this with the disappearance of the granule cells. There are certain features which I should like to point out in the cerebellum in this condition. One is the disappearance of the basket cells, which again is very unusual. In many conditions of degeneration of the cerebellum, the Purkinje cells drop out and leave the baskets, which may be hypertrophied. Another point is the curious swelling of the dendrites of the Purkinje cells; they are filled up with lipoid matter similar to that which you see in the nerve cells and, in fact, they may show more swelling than the actual cell body. With the neuroglia fiber stain, one sees masses of lipoid in the dendrite of a Purkinje cell, and sometimes up near the surface you see these masses with terminal argyrophilic fibrils running out in a curious star-shaped manner. There is also intense overgrowth of neuroglial fibers. That is almost the exact picture that was seen in this case, but there was still greater dropping-out of Purkinje cells so that very few remained.

That brings me to the question of the terminology of these conditions. I prefer what is being accepted in England now as the classification of these conditions, putting both the Bielschowsky and the Spielmeyer-Vogt groups together and calling them Batten type. Batten described them in 1903,[4] two years before either Spielmeyer or Vogt and 11 years before Bielschowsky, and with Mayou he later (1915) described the retina in this condition.

When you look at the retina in these patients, they fall into three quite sharply defined groups. The curious thing is that the retinal disease is so entirely different in cases in which the rest of the nervous system shows remarkably similar appearances. In a typical Tay-Sachs case you see a thinning-out of the nerve cell layer in the neighborhood of the macula, where it ought to be about 6 or 7 cells thick. There are large cells containing lipoid which are not ganglion cells; their nucleus is different and they appear to be phagocytes; the lipid is also seen in the outer part of the rods and cones. The other two nuclear layers of the retina are normal throughout the macular region. In eight cases, which so far as I know are the only ones in which the retina has been examined in the type of case we

are discussing today, the appearance is entirely different. The ganglion cells in the retina are in normal numbers; they may be rather swollen with lipid, but they are not very diseased, and certainly there is no great disappearance of them. The inner nuclear layer is also normal, but the outer nuclear layer fades out and disappears completely near the macula. In a case of a four year old child who could still see a few days before his death, there was a good deal of cerebellar symptomatology and very marked myoclonic twitching, which was the most striking thing about his clinical picture. He could still see in spite of the fact that he had no rods and cones at the macula. That, as I said, is an early case; in the other seven cases in the literature—(I am sorry to say there are only seven; there ought to be a great many more if people had taken the trouble to examine the retina more often)—there is the same picture, disappearance of the outer nuclear layer apparently starting from the region of the macula and spreading outward so that there are large areas at the back of the eye in which there is no outer nuclear layer.[5]

Now in the table which Dr. Aring presented, he also put down Kufs who dealt with a later age group. This is a very interesting group of cases because they have epilepsy, they may have myoclonus, but they may or may not be blind. One patient had had epilepsy for something like 15 years and died at the age of about 28, so that he started his illness at about the age of 13. The periodic acid Schiff method showed lipoid phagocytic cells in the ganglion cell layer of the retina, which seems to be otherwise normal. Another interesting point about these cases is that the degeneration of the nerve cells is not so universal. You may find it in the cerebellum and in the cortex but not in the basal ganglia, so that it differs from the children's groups both in the retina and in that peculiarity. Otherwise the nerve cells are similar and obviously contain galactolipids. Whether they also contain phospholipids or not, I do not know.

The only other point that I might mention is that one of the students asked about a disease which he called by my name; I do not know whether he was referring to a form of degeneration of white matter which I separated from the general group of Schilder's disease in 1933,[6] and more recently called *late infantile metachromatic leukodystrophy*. This disease has been missed frequently, although a few cases have turned up recently on the continent of Europe and one in Canada within recent years. Chiefly it has been missed because the white matter in that condition does not look sclerotic or gray or obviously diseased. When you make microscopic sections of it, you are struck by the poverty of nuclei which appear to have disappeared from the white matter, and some pathologists looking at this have considered it necrotic and have discarded the material as being autolytic; that is certainly the first impression it gives you. When you study it thoroughly, you see that there is a complete dropping out of interfascicular oligodendroglia in the white matter. The disease has another very peculiar feature in that the myelin disappears in the inverse order in which it is laid down. Any tracts which are present at birth tend to be spared. The first tracts which come along in the cerebrum after birth, such as the optic radiations, also tend to be spared, and this can be traced right down through the nervous system in a remarkable way so that you can almost tell what the date of maturation should be by the extent of degeneration in each tract. Recently we have evidence that this disease is associated with an abnormal quantity not only of glycolipid but also of other nonlipid polysaccharides in the white matter of the brain. At present this is as far as we can go as to its cause, but I think one is justified at any rate in separating this disease from the general group of Schilder's disease. These cases do not tend to go blind until the later stages of

the disease because the optic radiations are preserved. They may or may not have seizures; as far as I know, they never have myoclonus, but they always at an early stage have cerebellar symptomatology, so that there may be a relationship clinically to this case.

DR. M. A. BLANKENHORN: Are there any known anomalies of lipid metabolism in this disease?

DR. LANDING: At a recent national meeting of pathologists, it was reported that cases of Tay-Sachs have an abnormally high beta-lipoglobulin in their serum, if I recall correctly.

DR. EDWARD GALL: But it's not manifest in the histiocytic system of the body?

DR. LANDING: No.

DR. KURT TSCHIASSNY: I would like to ask for an explanation of the fact that this child responded with attacks to various acoustic stimuli and yet was deaf.

DR. GALL: The child was not completely deaf.

DR. JAMES MOULTON: In the preceding three generations of this child's family, there was no known Jewish ancestry; in fact, there was no known disease of the nervous system except for a recent stroke in her grandfather, who incidentally was a rather prominent physician. Amaurosis was not seriously considered during her lifetime. The child was seen by Dr. William Lennox about a year before she died, as far as I know, and he didn't consider amaurotic idiocy either. The first time that I saw her, the irritability of her nervous system resembled that of strychnine intoxication more than anything else that we considered. I would like to ask Dr. Greenfield two questions. The cells of the cerebral cortex were not all of the type of the balloon cells that one ordinarily associates with amaurotic family idiocy; in fact, many of them were very small. I wonder how to distinguish the lipoid changes in these cells from that of nonspecific lipoid damage that one may see in persons who are a long time dying, particularly when carried at toxic levels of medication for a period of a year and a half? This child was carried on very heavy doses of anticonvulsants. I also wonder if Dr. Greenfield would comment on the rather marked disseminated damage in the subcortical white matter in this youngster?

DR. GREENFIELD: The answer to the first question is very difficult, except that this child did have many cells which were distended; I don't say that every cell was distended by any means, but in the spinal cord, for example, the anterior horn cells were quite definitely more distended with lipid than I think you would see in a simple wasting disease. I don't think there is any distinction in the type of lipoid between what you get in a case like this and what you might get in such a case. Of course, the cerebellar picture would make a very remarkable distinction. You very seldom get that apart from this condition; it is almost pathognomonic of this condition.

The other question concerned the damage to the subcortical white matter. This is not unusual in this condition. I think it depends on disappearance of the deeper lying cells, the large pyramids of the fifth and sixth layers, and their replacement gradually by microglia and neuroglia, as certainly was very striking in this patient. I've seen it commonly in similar cases.

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CASE REPORT

Leukemia with Predominant Neurologic Manifestations

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A NUMBER of reports have appeared in the recent literature dealing with involvement of the nervous system in leukemia.[1–4] But while the incidence of neuropathologic changes has been estimated to be as high as 80 per cent, neurologic signs and symptoms have been observed only in about 20 per cent of cases. Moreover, such clinical manifestations were usually noted in the terminal phases of the disorder. Isolated cases in which the presenting symptoms were primarily neurologic have been reported by Schwab and Weiss,[2] Gauld,[5] Alajouanine et al,[6] Murphy and Brody,[7] and Kohut.[8] It is our purpose, therefore, to draw attention to this aspect of leukemia by reporting a case in which the clinical course was entirely dominated by the neurologic manifestations.

REPORT OF CASE

A 35 year old white male cyclotron engineer was admitted to Letterman Army Hospital on October 24, 1952. He had been in good health until September 9, 1952 when he suddenly began to experience pain and paresthesias at first in the left leg and later in both lower extremities. Soon after this, frontal headaches, impairment of vision, epileptiform attacks, ocular and facial palsies, and states of delirium developed in rapid succession. Examination in another hospital disclosed repeated pleocytosis in the spinal fluid, varying between two and five thousands cells per cubic millimeter, but no organisms were demonstrated.

Examination: On admission, the patient's temperature was normal. He was markedly confused and appeared to be in severe pain. There were rigidity of the neck and spine, gross evidence of bilateral ophthalmoplegia, and a peripheral type of left facial weakness. He was too resistive to permit a detailed examination until November 4 when he became somewhat more cooperative. At that time the following additional neurologic signs were elicited: amblyopia; 4 diopters of papilledema on the left, mild papilledema on the right; a larger left pupil, sluggish reaction of both pupils to light; complete absence of abduction and limited adduction and upward gaze of both eyes; hypalgesia of the left side of the tongue and lower lip; a positive Kernig sign; flaccid paralysis of the lower extremities; and absence of deep tendon reflexes in both legs and arms. A complete sensory examination was not possible but there was gross impairment of pain and temperature sensation in the lower extremities, most marked in the posterior sacral segments, with complete saddle anesthesia. There was paralysis of the bladder and rectal sphincters.

From Letterman Army Hospital, San Francisco. The statements and conclusions of the authors are the result of their own studies and do not necessarily reflect the policy or opinion of the United States Armed Forces.

Initial examination of the blood showed a normal proportion of red blood cells, a hemoglobin content of 15.6 gm., 125,000 platelets, and 8,150 white cells per cu. mm., of which 79 per cent were polymorphonuclears, 16 per cent lymphocytes, 4 per cent monocytes, and 1 per cent eosinophils, with an occasional myelocyte. Subsequent examinations did not show much variation from the above until January 1953 when the white count fell to 4,600 per cu. mm. and the smear was suggestive of monocytic leukemia. Several examinations of the spinal fluid revealed a total protein varying between 104 and 172 mg. per cent, and 1,650 to 2,000 white cells which were described as mononuclear forms showing frequent mitotic figures. A pneumoencephalogram revealed only slight dilatation and no shift of the ventricles.

Course: On the initial assumption that the condition was one of diffuse neoplasia of the meninges, whether glioma, sarcoma, or leukemia, the patient was given radiation therapy to the base of the skull and the cervical and sacral regions of the spine. With this treatment an immediate improvement set in. The headaches and the delirious episodes disappeared; some movement was regained in the lower extremities and there was return of the organic reflexes; the cranial nerve palsies disappeared with the exception of the visual impairment which persisted, as did the radicular pain of the lower extremities. Another examination of the spinal fluid on December 19 failed to reveal any of the abnormal cells previously found and the total protein had decreased to 104 mg. per cent. During the end of January 1953, however, small, discrete, purplish, oval, indurated papules appeared in the skin of the abdomen and extremities. The histologic diagnosis of a biopsy taken from the skin lesions was leukemia. By now, a blood smear was interpreted as compatible with monocytic leuekmia. On March 1 nitrogen mustard therapy was instituted but was discontinued on March 12, since the patient developed thrombocytopenia, leukopenia, and aplastic anemia. He was then treated with multiple blood transfusions, cortisone, and penicillin. However, his condition declined rapidly. Toward the end, multiple hemorrhages developed in mucous membranes and conjunctivae, and the patient passed bloody urine. He again became delirious and expired on March 23, 1953.

Necropsy: *Gross observations*: The skin showed diffuse jaundice, scattered hemorrhages, and myriads of maculopapular lesions. Pe-

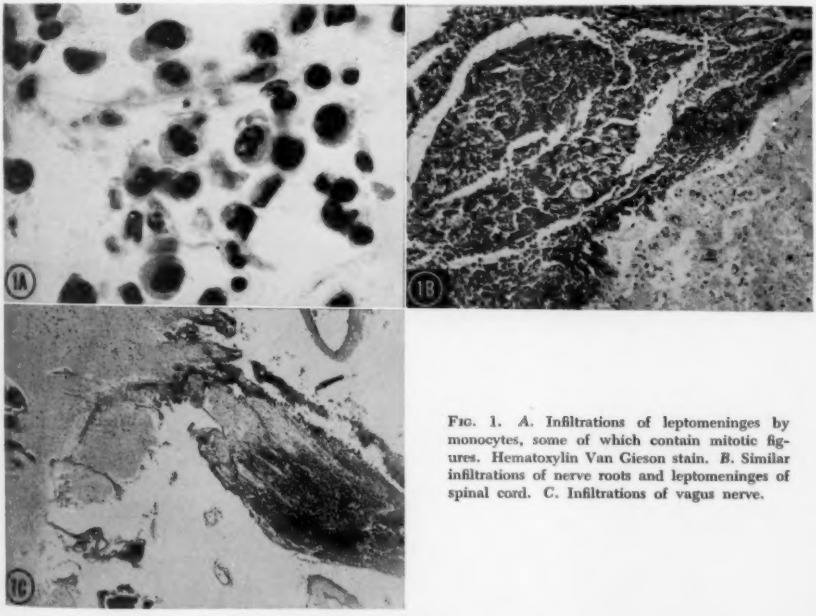

FIG. 1. *A*. Infiltrations of leptomeninges by monocytes, some of which contain mitotic figures. Hematoxylin Van Gieson stain. *B*. Similar infiltrations of nerve roots and leptomeninges of spinal cord. *C*. Infiltrations of vagus nerve.

techial hemorrhages were also found in the conjunctivae and oral mucous membrane. There was an indurated mass in the right scrotum. The peritoneal and pleural cavities were studded with hemorrhagic lesions. The heart was essentially normal. The lungs were edematous and contained hemorrhagic areas in each lobe of the right lung. There was moderate enlargement of the spleen, liver, and the cervical lymph nodes. The bone marrow appeared pale and more porous than normal. Scattered hemorrhages and occasional nodules were noted throughout the gastrointestinal tract, kidneys, and bladder. The indurated scrotal mass consisted of grayish-brown tissue which was firmly attached to the right testis and epididymis and replaced approximately one-half of the seminiferous tubules, the adjacent soft tissue being involved up to the base of the penile corpora cavernosa including a portion of the urethral bulb. The brain weighed 1,480 grams. There were scattered hemorrhages, both old and recent, in the leptomeninges. Coronal sections revealed diffuse hyperemia and moderate enlargement of the ventricles. There was marked thickening of the pia-arachnoid about the spinal cord and nerve roots, with matting together of the nerve bundles in the cauda equina region.

Microscopic observations: The most conspicuous change in the tissues and organs consisted of diffuse infiltration by monocytes. The cells were about 20 microns in diameter, with pale basophilic cytoplasm and dense basophilic nuclei which varied in size and shape, but were usually convoluted and contained many mitoses (figure 1A). They were found in the central nervous system, skin, pericardium and myocardium, aorta, lungs, spleen, cervical lymph nodes, bone marrow, gastrointestinal tract, liver, kidneys, urinary bladder, testes, adrenals, thyroid, and pituitary glands.

The most marked changes were observed in the following regions: In the central nervous system, a diffuse infiltration by mononuclear cells involved the leptomeninges and nerve roots of the entire cerebrospinal axis, being most marked in the cauda equina region (figure 2B). Of the cranial nerves, the optic, oculomotor, and vagus (figure 1C) were the most severely affected. The optic nerves and tracts (figure 2A) showed widespread degeneration and infiltration by fat-laden gitter cells. A combined degeneration of the dorsal and lateral columns was noted throughout the spinal cord (figure 2B). In the testes the abnormal cells were highly concentrated, widely separating atrophic seminiferous tubules and tubules of the epididymis (figure 3A). In the skin the cells infiltrated extensively the subepithelial areas about skin appendages and in the subcutis (figure 3B). The spleen and the cervical lymph nodes (figure 3C) were diffusely infiltrated by the cells, which obscured their normal architecture. The bone marrow was hypocellular, consisting mostly of the abnormal cells with only occasional precursors of erythrocytic or granulocytic elements. In the esophagus (figure 3D) and stomach there was extensive recent mucosal ulceration where mixed organisms, including spore-forming bacilli and fungus mycelia, were demonstrated. The peripheral blood contained similar cells with occasional mitotic figures and a rare mononuclear lymphocyte; the morphology of the erythrocytes appeared normal and platelets were rare.

COMMENT

Clinically, the case presented a diagnostic problem. The progressive neurologic pic-

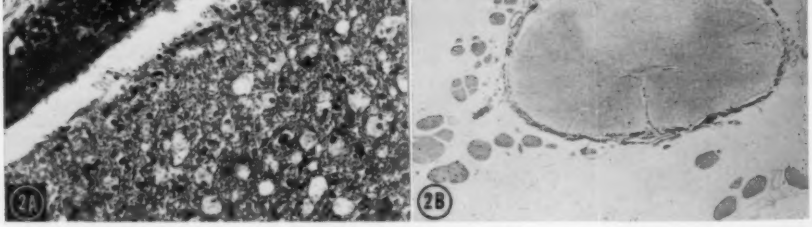

FIG. 2. *A*. Optic tract showing degeneration of its fibers and proliferation of gitter cells with monocytes in adjacent meninges. Hematoxylin-eosin stain. *B*. Combined degeneration of posterior and lateral columns of spinal cord. Hematoxylin Van Gieson stain.

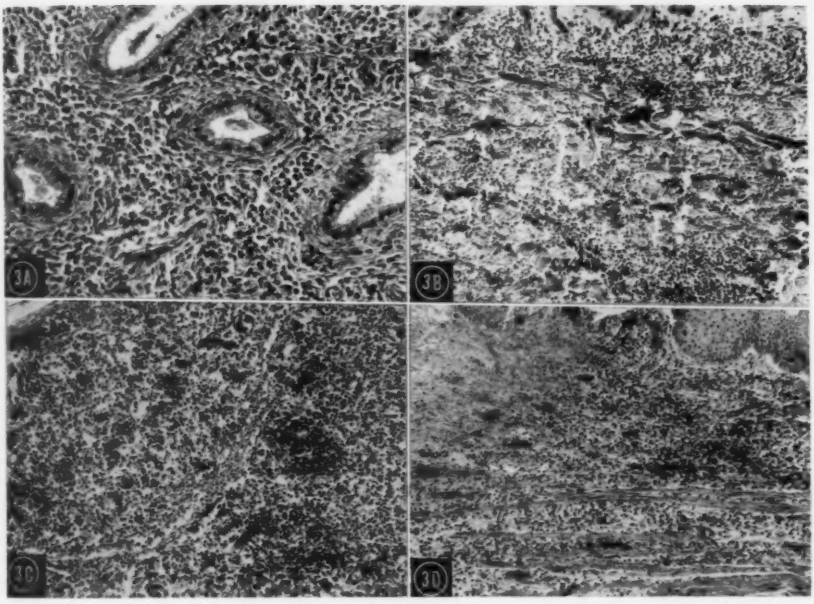

FIG. 3. *A.* Cell infiltration about tubules of epididymis. Hematoxylin-eosin stain. *B.* In skin. *C.* In lymph node. *D.* In wall of oesophagus showing ulceration of mucosa.

ture and the neoplastic cells in the cerebrospinal fluid pointed at first to a primary affection of the central nervous system. But while the condition was variously interpreted as diffuse glioma, sarcoma, carcinoma, or leukemia, none could definitely be verified. At no time was there evidence of hepato- or splenomegaly, lymphadenopathy, or leukocytosis to suggest leukemia. It was only toward the end of the illness when typical skin lesions developed and abnormal cells appeared in the blood that a diagnosis of monocytic leukemia was established. As such, a predominant neurologic disorder associated with aleukemic leukemia remains unique.

Pathoanatomically, too, the case was unusual. For while the hematopoietic system was also involved, the changes were universal and were particularly marked in the central nervous system. Also, there was absence of the usual findings described in the literature, for instance, metastatic foci within the nervous tissue of leukostasis, perivascular infiltrations, and hemorrhages. Rather, the infiltrating cells adhered closely to the spinal and cranial nerve roots and to the leptomeninges without penetrating beyond these into the underlying tissue. It appeared that the leukemic cells did not migrate through the blood stream, but proliferated in situ as was further confirmed by the presence of numerous mitoses. As such, the case suggests a form of leukemia which develops locally from undifferentiated mesenchyme. Another neuropathologic feature of this case was the degenerative optic neuritis and combined posterolateral myelopathy. Such findings, commonly noted in pernicious anemia, have been rarely observed in leukemia.

Therapeutically, the initial favorable re-

sponse to irradiation fully justified such a course of treatment, even though the diagnosis had not been first established.

SUMMARY

A case of monocytic aleukemic leukemia which followed a course of a primary neurologic disorder is reported clinically and pathoanatomically. It is suggested that the local proliferation of mesenchymal tissue in the nerve roots and leptomeninges accounted for the presenting neurologic manifestations at a time when the other clinical manifestations of leukemia were not apparent.

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■ If the transmission of sensitive impressions does not take place along the posterior columns, it remains to be found what is the channel of this transmission. Is it the gray matter or some part of the lateral or anterior columns, or all of several of these constituents of the spinal cord? As regards the lateral columns, if we divide them transversely in the dorsal region, we find that sensibility, instead of being lost, seems to be increased in the two posterior limbs. But if, in performing this experiment, the knife goes farther than the limits of the lateral columns, and divides a part of the central gray matter on the two sides, sensibility is then diminished in the two posterior limbs. From these experiments, and from another one, which consists in a transverse section of the whole spinal cord except one of the lateral columns, it results that these columns, like the posterior, are not the channels of transmission of any part of the sensitive impressions to the encephalon.

C. E. Brown-Sequard in *Lectures on the Physiology and Pathology of the Central Nervous System*, published in 1860.

CASE REPORT

Choroidal-Lesser Galenic Arteriovenous Malformations

James Peter Murphy, M.D.

INVESTIGATION of the embryologic development of the cerebral circulation indicates that persistence of abnormal arteriovenous communication between the choroidal arteries and the galenic venous system should be of relatively frequent occurrence.[1] Actually, the reported clinical incidence of such vascular anomalies is rare, and the great cerebral vein has usually been involved in gross fashion.[2–4] The following two case reports concern cerebral vascular malformations in which arterial inflow was from the anterior choroidal artery, and venous drainage occurred to the lesser vein of Galen or its tributaries.

CASE REPORTS

Case 1.—A 22 year old white female was examined on March 28, 1951, at which time she complained of unbearable headache of recent onset and stiffness of the neck. She had suffered from minor and major convulsive seizures accompanied or preceded by cephalalgia since the age of 16. These attacks were only poorly controlled with anticonvulsant medication. Several siblings had been born with cranial or cerebral defects.

Physical examination disclosed only slight nuchal rigidity and no neurologic abnormalities. Surprisingly, spinal puncture withdrew uniformly bloody fluid. The patient was admitted to the George Washington University Hospital. An electroencephalogram was generally abnormal, with a slow spike focus in the right anterior temporal area. Accordingly, carotid angiograms were made; on two separate occasions roentgenograms disclosed elevation of the right middle cerebral artery. On April 11, 1951 craniotomy was performed and 40 cc. of old blood were aspirated from the right temporal lobe. What was thought to be a potentially bleeding vessel in the wall of the hematoma cavity was fulgurated.

Recovery was prompt but temporary. Several days later a bout of psychomotor convulsive seizures was followed by frank evidences of intracranial bleeding. The right common carotid artery was ligated. The patient was discharged from the hospital, only to be readmitted two weeks later because of recurrence of her original complaints of headache and convulsions. Spinal puncture again showed bloody fluid. Right frontotemporal craniotomy was undertaken once again.

At operation it was evident that repeated bleeding had occurred into the right temporal lobe, which was excised anteriorly. The vascular membrane which constituted the capsule of the hematoma was dissected medially to the vicinity of the anterior choroidal artery, which was grasped and coagulated. Posteriorly it seemed certain that the lesion drained into a minor tributary of the galenic venous system. The angiomatous sac was removed completely.

From the department of neurology and neurological surgery, George Washington University School of Medicine, Washington, D. C.

After this procedure recovery was rapid and her condition remains stable. At last examination on October 9, 1952 no neurologic signs were evident and the patient was free from seizures on an anticonvulsant medication. There has been no recurrence of intracranial hemorrhage.

Case 2.—A 16 year old previously healthy girl suddenly had a grand mal convulsion while in school, becoming unconscious and paralyzed shortly thereafter. Examination at the Garfield Memorial Hospital, Washington, D.C., revealed her to be stuporous and totally paralyzed and insensate on the left. The neck was stiff and Kernig signs were elicited. The spinal fluid was grossly bloody.

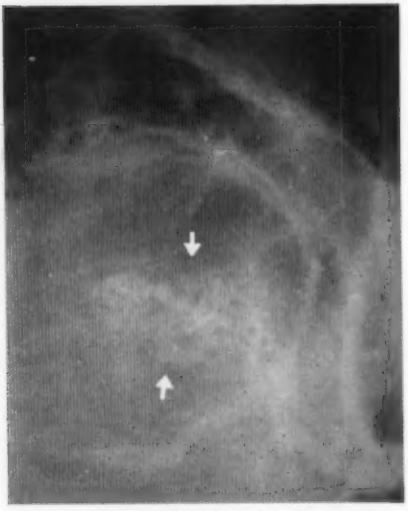

FIG. 1. Arteriovenous malformation (between arrows) of choroidal-galenic type. Anteroposterior arteriogram; anterior cerebral artery below, middle cerebral artery above. (From Murphy, J. P.: Cerebrovascular Disease. Used with permission of Year Book Publishers, Inc.)

Right carotid angiography on March 25, 1954 demonstrated a large arteriovenous malformation which occupied a major portion of the thalamus and basal ganglia (figure 1). In a lateral film the lesion could be seen to drain into the lesser vein of Galen or one of its tributaries. On April 1, 1954 right parietal craniotomy was performed. A sizeable blood clot, liquid and solid, was removed from the vicinity of the internal capsule. All of the malformed and anomalous blood vessels surrounding the clot were coagulated and Gelfoam was packed in the interior of the hematoma cavity.

The postoperative course was precarious and stormy. Signs of decerebrate rigidity developed and it became necessary to perform tracheotomy. Eventual clinical improvement permitted discharge from the hospital. At present the patient is able to walk with slight assistance; the hemiplegia has persisted. She has been free from convulsions on an anticonvulsant medication, and there has been no recurrence of intracranial bleeding.

SUMMARY

Two cases are reported of arteriovenous malformation involving the vascular fields of the anterior choroidal artery and the lesser vein of Galen or tributaries. Both patients were treated surgically, with an excellent clinical result in one instance and only preservation of life and prevention of further hemorrhage in the other. It is suggested that so-called angiomas of the basal forebrain nuclei, a recognized cause of cerebral apoplexy in the young, may actually represent choroidal-galenic arteriovenous malformations.

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CORRECTION

In Dr. Lewis P. Rowland's article, "Prostigmin-Responsiveness and the Diagnosis of Myasthenia Gravis," pages 612-624 of the September 1955 issue of NEUROLOGY, the correct spelling of the drug should have been Prostigmin. This drug is a product of Hoffmann-LaRoche, Inc., Nutley, New Jersey.

Neurology

BOOK REVIEWS

Clinical Neurology

A. B. Baker, M.D., Editor. 1955. New York: Paul B. Hoeber, Inc. Three volumes, 1,960 pages. $60.00.

THIS monumental work is the brainchild of Dr. A. B. Baker, the culmination of 11 years' consecration by an indefatigable worker. His inspired effort has brought together contributions from 65 authors, representing wide selection of students of clinical neurology and its allied disciplines. This extensive work, the first of its kind in this country, covers every phase of neurology in a well-organized framework.

The first 350 pages of volume 1 are concerned with diagnosis and diagnostic methods. There are superb chapters on case taking and neurologic examination, roentgenography, electroencephalography and electrophysiology, ophthalmology, cerebrospinal fluid, psychologic testing (not usually covered in neurologic texts), and physiology of cerebral localization. From this background of modern clinical neurologic methodology, there follow in logical order chapters devoted to clinical disorders. Agnosias, apraxias, speech, and aphasia are ably presented. The remainder of the chapters of volume 1 concern such topics as intracranial neoplasms, intracerebral vascular disease, extracerebral vascular disease, cerebral anoxia, headache, infections of the dura, meningitis, brain abscess, diffuse suppurative encephalitis, and viral encephalitis.

Chapters in volume 2 are devoted to secondary forms of encephalitis, neurosyphilis, cerebral intoxications, drug and alcohol addiction, craniocerebral trauma, epilepsies and convulsive disorders, demyelinating diseases, diseases of the brainstem and cranial nerves, spinal cord anatomy, physiology, localization, and clinical considerations, as well as syringomyelia and related conditions, spinal cord tumors, and protruded intervertebral disks. Especially meritorious are the chapters on the extrapyramidal diseases, disorders of the hypothalamus and the pituitary gland, and one on the cerebellum, which includes the anatomy and modern concepts of cerebellar physiology and clinical disorders.

In volume 3 are to be found other chapters on spinal cord disorders, chapters devoted to peripheral nerves, neuralgias, neuromuscular disorders, anomalies of the nervous system, infantile cerebral palsy, vegatative nervous system, nutritional disorders, and endocrine disturbances. Of special interest and evidence of the completeness of the text are the chapters on neurologic complications of internal diseases, neurologic rehabilitation, psychologic aspects of neurology, and the final chapter on genetic aspects of neurology.

The publication of these volumes may well be regarded as a landmark in American neurologic progress. In presenting the various disorders resulting from dysfunction of the nervous system, there has been cor-

relation with modern neurophysiologic and anatomic concepts. The illustrations have been well chosen and are excellently reproduced; the anatomic diagrams are clear and intelligible. Each chapter has extensive documentation and references to the literature. The subject index is in the third volume and is easy to use.

The editor, the contributing authors, and the publisher are to be congratulated.

M. G. M.

The Spino-Cerebellar Degenerations

J. G. Greenfield, M.D., F.R.C.P. 1954. Springfield, Illinois: Charles C Thomas, Publisher. 112 pages. $4.00.

This monograph presents an integrated discussion of the group of spinocerebellar degenerations. The approach is a clinical and a very useful one.

Quite properly there are presented Friedreich's ataxia and its variants, Charcot-Marie-Tooth atrophy, Roussy-Levy syndrome, hereditary cerebellar ataxia, late cortical cerebellar atrophy, olivopontocerebellar atrophy, and dentatorubral atrophy. The material is mobilized skillfully, comparisons and contrasts are indicated, and, especially valuable to earnest inquirers, there are complete references to the many eponyms that still clutter this field.

There is a brief anatomic and physiologic introduction. This includes the recent work of Eldred, Granit, and Merton on a "feedback" efferent system to the sensory receptor muscle spindles, indicating the probability of a self-regulating tonus control system. The section on anatomy may be too brief; some details are omitted. Thus the vestibular fibers to and from the cerebellum are not mentioned. The book is not illustrated.

This is an authoritative work, concisely and well written. It is recommended for the neurologist's library.

A. R. V.

The Clinical Examination of the Nervous System

G. H. Monrad-Krohn, M.D. Tenth edition. 1955. New York: Paul B. Hoeber, Inc. 428 pages. $7.50.

The fact that Monrad-Krohn's book on *The Clinical Examination of the Nervous System* has undergone ten revisions in 24 years suggests two things. One of these is that there has been a constant demand for this book by students and physicians; the other is that the author has attempted to keep abreast of advances in neurologic diagnosis. The major changes in the present edition deal with the supplementary methods of examination. The author has rewritten the chapter on electroencephalography and has added small sections on electromyography, pneumoencephalography under x-ray control, and vertebral angiography.

The major contribution of this work has been the clinical presentation of the fundamentals of neurologic diagnosis, based on Professor Monrad-Krohn's large personal experience. He has amplified this from year to year, with broadened observations and newer concepts. The sections which deal with the technical supplementary methods of examination give the general principles of the various procedures, but cannot be considered to be as authoritative or as complete as detailed texts on these technics. They do, however, add to the value of the book and contribute toward making it a reliable compendium on the various aspects of neurologic diagnosis – from both the clinical and the laboratory aspects.

R. N. DeJ.

Neurology

S. A. Kinnier Wilson, M.D., D.Sc.(Edin.), F.R.C.P., edited by A. Ninian Bruce, F.R.C.P.(Edin.), D.Sc.(Edin.), M.D., F.R.S.(Edin.). Second edition. 1955. Baltimore: Williams and Wilkins Company. Three volumes, 2,159 pages, 279 illustrations. $37.50.

THE first edition of this book was published in 1940 and has since been considered to be the most important and most encyclopedic survey of clinical neurology available in the English language. Although it was based on notes, references, and a partially completed manuscript to which Dr. Wilson devoted a large part of his time during the last ten years of his life, and thus summarized his extensive clinical experience, it had not been completed at the time of his death in 1937. The final preparation for publication was done by Dr. Bruce. The first edition has long been out of print, and there has been a repeated demand for a new edition. The second edition, now available, was also prepared by Dr. Bruce.

This new edition, like the first, offers a comprehensive survey of our knowledge concerning and the literature available on clinical neurology. Certain additions have been made. Sir Russell Brain has contributed a noteworthy chapter on aphasia, apraxia, and agnosia, and Dr. Samuel Nevin has reviewed the chapter on neurosyphilis and has rewritten the section on treatment. Unfortunately, however, even though the statement is made in the preface that "endeavour has been made to include summaries of the more important neurological advances," the text has not been brought up-to-date to the degree that had been anticipated by the many neurologists who were anxiously awaiting the publication of this new edition. The book follows the same outline and stresses the same classifications of neurologic disease that were incorporated in the first edition, and many of the latter are more or less outdated at this time. The advances during the past 15 or perhaps 20 years are mainly brought out by brief references to the literature, without any correlation with actual clinical experiences on the part of the editor. Treatment, which has been one of the outstanding contributions of contemporary neurology, is still minimized.

These statements may be amplified by a few illustrations. In the treatment of the meningitides there are several references regarding the use of the sulfonamides, mainly dating between 1939 and 1944, but only the most brief mention of the antibiotics; most of the conclusions regarding prognosis allude to the period before the institution of either. Under the treatment of tetanus there is only a short statement regarding curare and Myanesin, stressing mainly the dangers of these preparations. Under Parkinson's disease there is but a single reference to surgical measures which, although they have not led to any definite therapeutic advance, have contributed markedly to our knowledge of the underlying neuroanatomic and neurophysiologic basis of the disorder. The subject of intracranial aneurysms is treated most briefly. Many current measures used in the therapy of cerebrovascular disease are not even mentioned, including physical rehabilitation measures which are so important today. Under epilepsy, electroencephalography is discussed most briefly; as much space is devoted to the bromides as to all other drugs mentioned; the reference to surgery consists of one sentence taken directly from the first edition; there is no discussion whatever of the recent advances in knowledge of temporal lobe seizure mechanisms and treatment.

This book is still an excellent reference work, especially for the older and fundamental literature in neurology. It is in many respects a reprinting rather than a new edition. It is regretted that editor has not brought up-to-date the many recent advances in neurologic theory, diagnosis, and treatment.

R. N. DE J.

**The Pyramidal Tract—
Its Status in Medicine**

Arthur M. Lassek, Ph.D., M.D. 1954. Springfield, Illinois: Charles C Thomas, Publisher. 166 pages. $4.75.

HERE is a little book to read when one feels especially smug about his knowledge of the central nervous system. This is a rather controversial monograph on the origin, course, distribution, and function of fibers contained in the fields of the lateral anterior white matter of the spinal cord, the medial anterior part of the medulla, the basis pontis, the basis pedunculi, and the internal capsule, generally referred to as the pyramidal tract, and perhaps better called the pyramidal bundle or fasciculus. The author sets out to eliminate the generalization that the "pyramidal tract is the sole pathway for volitional movement" and to prevent the error of considering the pyramidal tract apart from sensory mechanisms. His concepts are presented forcefully.

Data from the author's own studies and from the literature are marshalled to present the startling lack of information about almost every aspect of the pyramidal tract. While the iconoclastic phase of the work is prominent, the clinician will find that he is not too greatly disturbed. He will almost surely revert to the truly comprehensive but conveniently nonspecific term "upper motor neuron" as the best way out of uncertainties. The latitude of just what may be included in the "upper motor neuron" permits him to readily assimilate the divergent functional alterations that appear when one attempts to specify too accurately a given anatomic pathway. So when the author finds that he is not able to establish a syndrome of the pyramidal tract alone, the reader will not necessarily find any need for perturbation.

The book is written in an orderly manner, with a presentation of the historical background and a discerning selection of the extensive literature. Each chapter contains a summary, and there are concluding chapters presenting the chronology of basic pyramidal tract investigations and of subhuman experiments on the pyramidal tract.

A. R. V.

1955 Medical Progress: A Review of Medical Advances During 1954

Morris Fishbein, M.D. 1955. New York: Blakiston Division, McGraw Hill Book Company. 346 pages. $5.00.

THIS IS THE THIRD VOLUME in a series which began in 1953 and is edited by the well known author, Doctor Morris Fishbein. This volume comprises chapters by a distinguished panel of American physicians.

There are some 20 fields in all covered in this volume. It is disturbing to note that an editor of Dr. Fishbein's scope has overlooked the inclusion of neurology. The chapters follow most of the usual great divisions of clinical medicine such as obstetrics and surgery, and there are also chapters on gastroenterology, allergy, diabetes, rheumatic diseases, nutrition, and even liver diseases. One cannot help but be disappointed and question the value of a book which has such a great scotoma in the knowledge that it covers. This deficiency in the book is well exemplified in a chapter on new drugs where Oxytocin and the suppressants, Diamox and chlorpromazine, are discussed. There is no reference to the newer therapeutic agents in neurology. This volume has very little to offer the neurologist.

F. M. F.

NEWSLETTER AMERICAN ACADEMY OF NEUROLOGY

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OCTOBER, 1955

Preliminary Reunion Held in Brussels In the scholarly calm of the University Foundation (la Fondation Universitaire), in Brussels, the executive committee, composed of official delegates of national neurologic societies in most countries throughout the world, convened in a preliminary reunion (Sept. 6-8) to structure a tentative program for the Sixth International Neurological Congress to be held in Brussels in 1957. Joining them in conference were international representatives of several allied but autonomously organized neurologic groups: Sir Geoffrey Jefferson (neurologic surgery); Armando Ferraro (neuropathology); A. E. Walker (epilepsy); Henri Gastaut (electroencephalography and neurophysiology). Purpose of these joint sessions was to bring together the Sixth International Neurological Congress and international congresses of allied disciplines into a combined gathering, meeting simultaneously under a coordinated program which would provide major symposia on topics of general interest to all groups and minor symposia on topics of more highly specialized interests. The result of the sessions was the formation of the international congresses of neurologic sciences, to be held in Brussels during the latter part of July 1957. They will comprise the Sixth International Neurological Congress, the Third International Congress of Neuropathology, the Third International Congress of Electroencephalography and Neurophysiology, the First International Neurosurgical Congress, and the International League Against Epilepsy.... The sessions in Brussels were conducted in a spirit of cooperation and paced with unique precision, thanks to the deftness and administrative skills of the Belgian committee, particularly Prof. van Gehuchten, Dr. Ludo van Bogaert, who shouldered the largest portion of the organizational load, and Prof. Paul Martin.

New Officers And Program Following a report by Prof. Almeida Lima on the Fifth International Neurological Congress (Lisbon, 1953), officers were elected for the Sixth Neurological Congress, which will serve as the organizational focal point for the

combined congress, previously mentioned: Professor Divry, honorary president; Prof. R. A. Ley, honorary vice-president; Prof. F. Bremer, first vice-president; and Drs. J. Titeca and R. A. Ley, treasurer and editor of transactions, respectively.... Elected to serve as secretary-general, and to whom all communications should be sent, is Dr. Ludo van Bogaert, Institut Bunge, 59, rue Philippe Willoit, Berchem-Anvers, Beglium.... Three major symposia of general interest, together with their respective chairmen, already have been selected: states of consciousness (Sir Geoffrey Jefferson, England); extrapyramidal disorders (Prof. H. Garcin, France); and multiple sclerosis (Prof. H. Houston Merritt, U.S.A.).

Merritt Elected Vice-President for U.S.A. H. Houston Merritt was elected vice-president to head the U. S. national delegation at the 1957 International Neurological Congress in Brussels. In this capacity he succeeds Henry Alsop Riley, who has been a towering figure of leadership in the organization of previous international neurologic congresses (Bern, Copenhagen, London, Paris, Lisbon), and who, at the Brussels reunion, was elected an honorary president to join the ranks of such notables as Professors G. Guillain, Th. Alajouanine, Andre-Thomas, Egas Moniz (Nobel Laureate), Antonio Flores, and Sir Gordon Holmes. Also named as honorary presidents were professors G. H. Monrad-Krohn (Norway) and Knud H. Krabbe (Denmark).

Belgium Hospitality At Its Best The delegates to the reunion were given a cordial welcome by the Belgium National Committee, first at a buffet reception at the University Foundation (Sept. 6), and later at a banquet (Sept. 7) in the historic Maison d'Erasme (House of Erasmus--outstanding humanist of the Renaissance). Here five courses of delectable dishes were served, with rare vintages of sherry Delaforce, champagne Boizel, port His Majesty, and brandy "beyond age"--all poured from magnums. Brief but spirited speeches of oratorical elegance by Professors van Gehuchten, Monrad-Krohn and others completed the memorable evening.... The final morning of the reunion was devoted to visits to hospitals in Brussels.

Neurosurgeons Form International Federation Preceding the preliminary reunion of the Sixth International Neurological Congress in Brussels, representatives of national neurosurgical societies from many countries held a meeting to organize an international congress of neurologic surgery. The result of this meeting was the formation of the International Federation of Neurosurgeons (title still tentative), the objectives of which are to further the science and practice of neurologic surgery throughout the world, to promote international goodwill, and

particularly, to organize neurosurgical congresses which will meet in conjunction with the international neurologic congresses.... The present officers of the federation are: honorary presidents, Professors H. Olivecrona, Wilder Penfield, D. Petit-Dutaillis, and P. Martin (other honorary presidents may be added); president, Sir Geoffrey Jefferson; vice-president, Prof. A. E. Walker; secretary-treasurer, Dr. M. David; assistant secretary-treasurer, Dr. W. B. Scoville; treasurer, Dr. A. Devic; assistant treasurer, Prof. A. Iniguez; and editor of transactions, Prof. H. Krayenbuhl.

Neuropathologists Meet in London The Second International Congress of Neuropathology met in London (Sept. 12-17), under the presidency of Dr. J. Godwin Greenfield, honorary consultant to the National Hospital, Queen Square. The congress was convened (Sept. 12) in the Great Hall of the Royal College of Surgeons by Dr. Mario Gozzano (Rome), president of the First International Congress of Neuropathology, who turned the meeting over to Dr. Greenfield. Following an exchange of welcomes, Sir Henry Dale, Nobel Laureate for his work on the chemical transmission of the nerve impulse, remarked on modern trends in neuropathology in the direction of histochemistry and physiology, from the study of visible structural changes to the invisible, and then declared the congress officially open. After votes of thanks and introductions of the chairmen of national committees from each country to Sir Henry, the scientific sessions began at 10:35 a.m. (Sept. 12).... The entire program of the congress was conducted with an efficiency and dispatch rarely seen, much of the credit for which belongs to Dr. W. H. McMenemey, secretary-treasurer, who, in the words of Sir Russell Brain, "served as a coordination center more efficient than the cerebellum with reverberating circuits which never cease."

Comprehensive Program While comprehensive, the scientific program provided presentations and discussions of a variety of topics, including the pathology of involuntary movement, cytochemistry of the neuron, cerebral tumors, aspects of mental disease, encephalitis, granulomas and reticuloses, blood-brain barrier, trauma, and miscellaneous subjects. A well-chosen array of exhibits and films supplemented these presentations. Abstracts of the papers presented at the congress have been published in Excerpta Medica, Vol. 8, No. 9, (Sept. 1955). .... Highlighted in the afternoon of the third day of the congress (Sept. 14) was a joint symposium of neuropathologists with neuroradiologists (4th symposium neuroradiologicum) on tentorial herniation, under the chairmanship of Paul Bucy (Chicago) in

collaboration with co-chairmen: P. Martin (Brussels), A. Lima (Lisbon), J. G. Greenfield (London), and J. W. Bull (London).

Formal Receptions Formal receptions occupied every evening of the congress, beginning Monday (Sept. 12) with a reception at Lancaster House, St. James's, to meet the Right Honourable Iain Macleod, M.P., Minister of Health, and Mr. J. N. Browne, C.B.E., M.P., Joint Parliamentary Under-Secretary of State for Scotland; followed on Tuesday by a buffet supper at Apothecaries Hall, graciously offered by the British members of the congress; and on Wednesday evening by a reception given to the delegates by the president and fellows of the Royal College of Physicians of London, in which full evening dress, decorations, and academic robes added color to the historic occasion.

Banquet Held at Mansion House The banquet of the congress was held in the Mansion House, built between 1739 and 1753, which now serves as the residence of the Lord Mayor of London, his family, and entourage. Following the banquet and toasts to Queen Elizabeth and other members of the royal family by Dr. Greenfield, speeches were made by Prof. Folke Henschen with response by the Lord Mayor locum tenens, Sir Noel Bowater; by Sir Russell Brain, president of the Royal College of Physicians, with response by Dr. Ludo van Bogaert; by Prof. A. C. P. Campbell with response by Sir Ernest Gowers, who is chairman of the board of directors of the National Hospital, Queen Square, and son of the famous English neurologist, Sir William R. Gowers (1845-1915).... The final reception was given on Friday by the vice chancellor of the University of London and Mrs. H. R. Robinson, in the Senate House, University of London.

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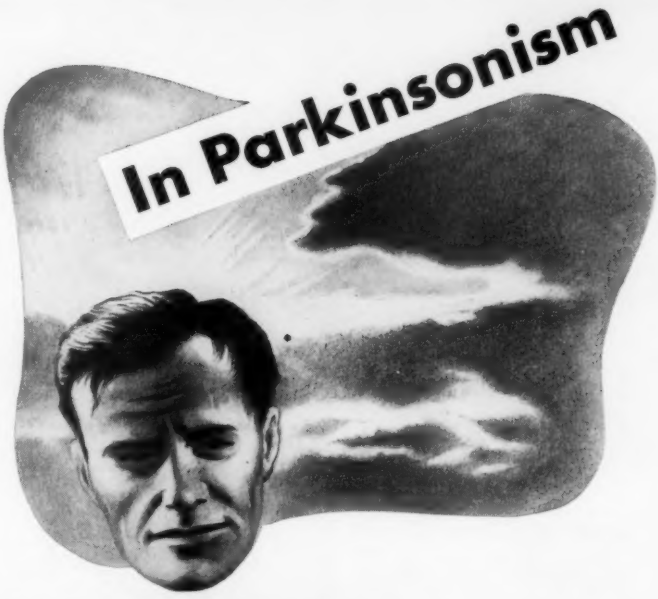

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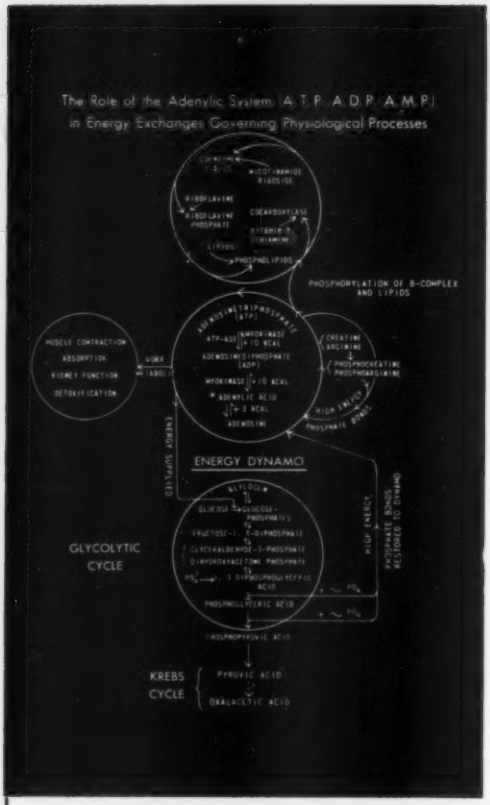

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